ORAL CONTRACEPTIVES AND RHEUMATOID ARTHRITIS: FURTHER EPIDEMIOLOGIC EVIDENCE FOR A PROTECTIVE EFFECT

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ORAL CONTRACEPTIVES AND RHEUMATOID ARTHRITIS: FURTHER EPIDEMIOLOGIC EVIDENCE FOR A PROTECTIVE EFFECT

PROEFSCHRIFT

TER VERKRIJGING VAN DE GRAAD VAN DOCTOR IN DE GENEESKUNDE
AAN DE ERASMUS UNIVERSITEIT ROTTERDAM
OP GEZAG VAN DE RECTOR MAGNIFICUS
PROF. DR. J. SPERNA WEILAND
EN VOLGENS BESLUIT VAN HET COLLEGE VAN DEKANEN.
DE OPENBARE VERDEDIGING ZAL PLAATSVINDEN OP
WOENSDAG 30 MAART 1983 DES NAMIDDAGS
TE 3.45 UUR

DOOR

JAN PAUL VANDENBROUCKE

GEBOREN TE LEUVEN

Promotoren:	Prof. Dr. H.A. Valkenburg Prof. Dr. A. Cats
Co-referenten:	Prof. Dr. H.J. van der Molen Prof. Dr. M.P. Vessey

"Whether my observations and opinions be disproved or supported, I shall be equally satisfied. Truth is the prize aimed for; and, in the contest, there is at least this consolation, that all the competitors may share equally the good attained"

D.J. Corrigan
Aneurysm of the aorta
The Lancet 1829;I:586–90

"Consider the implications of the fact that more than fifty million women worldwide take regularly for contraceptive purposes a combination of hormones that essentially cuts off the function of their own ovaries"

B. MacMahon
Strengths and Limitations of Epidemiology
The National Research Council
National Academy of Sciences, Washington DC 1979

For Christina, Karianne and Myriam

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DEDICATION

This thesis would not have been possible without all my educators before and during the investigation, and all those people who helped me with the investigation itself.

Two people contributed the most to my understanding of epidemiology. O.S. Miettinen, Professor of Epidemiology and Biostatistics at the Harvard School of Public Health, guided me through a memorable year in Boston in 1978/79; he taught me the principles of problem conceptualisation, study design, analysis and inference in epidemiologic research. That I have had the chance to be formed by this contributor to epidemiologic methodology, is still reflected in my daily professional activities. H.A. Valkenburg, Professor of Epidemiology at the Erasmus University of Rotterdam, taught me the fifth principle of epidemiology, the one which stands right in the middle of the previous four: the practice, i.e. the process of collecting data on populations, and the translation of theoretical concepts into reality. More than that, he gave me the opportunity to work in his department. Hans, as we call him, has that rare quality of being a departmental head who places so much trust in his collaborators that he gives them a great degree of freedom in their research undertakings, yet always has an open door and mind when advice is needed, and continues to support them in times of trouble or adversity.

During my medical and philosophical undergraduate and graduate training and during my specialisation in internal medicine, I learned from too many to mention here. Let me only highlight Prof. Dr. J.V. Joossens, who instilled in me my first enthusiasm for epidemiology and supported all of my applications for training and grants.

The very first people to make this investigation possible were the rheumatologists: J.P. Boersma, Prof. Dr. A. Cats, Dr. J.J.M. Festen, A.P. Hartman, O.Huber-Bruning, Dr. J.J. Rasker and Dr. J. Weber. Their reaction to the study proposal was enthusiastic and generous. The registration data which they had compiled over many years enabled me to entertain the concept of the present investigation, which was only possible because of their multicenter collaboration. Let me also thank all of their friendly secretaries and other administrators, such as the medical registration departments who helped me to trace patients. Next, there are the patients who responded in such favourable numbers to our request for information. When the first questionnaires came in, it was moving to see how many entered details about their personal lives in an effort to contribute to a scientific undertaking.

Whom of my colleagues from the Institute of Epidemiology should I thank first? Bert Hofman for his stimulating discussions, who more than once saw through my data more clearly than I did? The "computer boys", Dr. Leo van Romunde, Bram van Laar and Leo Muller, for being small system adepts who implemented

not only major statistical packages, a logistic regression program and a general data management program but also a text processor and photoprint program with which this text is written – and for always being (too) ready to help in times of trouble? The department's secretary, Cilia Kuynders, for caring for everybody with practical advice? Several people helped me with the daily management of the investigation: in the beginnning Loes van Zuuren-Soek and Lilian Verwey-Koopmans, and later Yvonne Jongepier-Geerdes who managed the final administration and prepared with considerable skill the tables and the manuscripts which are part of this thesis. The English language was reviewed by Mrs. G.P. Bieger-Smith.

In the end, it is the education by my parents, which brought me here. To my father I owe an education in the spirit of scientific inquiry and explanation, which was always tempered by deep human compassion and understanding. The education provided by my mother ranged from helping with my first talk before a class in primary school to enlivening the principles of genetics of medical school books with illustrations from her own work on the Rhesus factor. To both my parents I owe never-failing support which continues until this day.

Finally, I thank my wife, Christina, for her quiet steadiness and because we were always able to agree on who should work during which part of the weekend, and our daughters Karianne and Myriam for asking at night to tell the bedtime story of daddy's booklet again.

CHAPTER I
INTRODUCTION

I.1 Motivation and background

An investigation of the association between the use of oral contraceptives and the occurrence of rheumatoid arthritis is the subject of this thesis. The investigation was prompted by two reports from the literature. First, in 1978 an unexpected by-product of the Royal College of General Practitioner's Study on Oral Contraception was published in The Lancet (Wingrave and Kay 1978): the incidence of rheumatoid arthritis in women who used "the pill" was about one-half that found for women who had never used oral contraceptives. Second, in 1980 the American Journal of Epidemiology published a report from the Mayo Clinics (Linos et al. 1980) showing that the incidence of rheumatoid arthritis among women living in Rochester, Minnesota, had decreased since the early 1960s, and that this decrease coincided with the general increase of the use of all kinds of female hormones, but particularly the contraceptive pill.

Rheumatoid arthritis is generally regarded as a non-killing disease – although its clinically severe forms reduce life expectancy by several years (Uddin et al. 1970, Allebeck et al. 1981, Rasker and Cosh 1981, Abruzo 1982). It can certainly be a severely crippling disease. A conservative estimate of its prevalence among middle-aged women in industrialised countries is about 2 per cent (Linos et al. 1980, Allander and Bjelle 1981, Hochberg 1981). A halving in incidence could yield a similar reduction in prevalence; if confirmed this means a dramatic reduction in human physical suffering with obvious consequences as far as society's cost-benefit calculations for oral contraceptives are concerned. Moreover, the clue that synthetic female hormones somehow offer protection against rheumatoid arthritis could lead to further queries into the immunopathogenesis of the disease.

Confronted with these literature reports and their implications, the author of the present study proposed that neither the single follow-up in Great Britain, nor the monitoring of secular trends by the Mayo Clinic's

records, was sufficient proof of the existence of a protective effect of oral contraceptives or other oestrogen use against rheumatoid arthritis. However, if a clear negative association can be observed in giant follow-up and secular trend studies like those mentioned above, a case-control study that would be much quicker and easier to perform should easily show the same. In addition, a case-control study with the specific single aim of studying the association between oral contraceptives and rheumatoid arthritis would permit proper identification and control for potential confounding factors.

At the Department of Epidemiology of the Erasmus University of Rotterdam a diagnostic rheumatology registry is maintained. This registry covered several of the larger outpatient and inpatient clinics of the Netherlands in 1978 and 1979. The aims were both scientific research and patient file management. The registry contains no information on the use of oral contraceptives, but it constitutes an unique source to mount a case-control study on rheumatic disease: it includes hundreds of cases of young women with rheumatoid arthritis and thousands of potential controls with diverse musculo-skeletal disorders. A second source of information about the pill and its relation to rheumatic diseases was the data from the EPOZ study, which were readily available on computer tape at the Department of Epidemiology. EPOZ is a Dutch acronym that stands for Epidemiological Preventive Investigation ('Onderzoek') Zoetermeer, a prevalence survey of chronic diseases and their determinants in 10,532 inhabitants of a single community in the Netherlands. In this survey information was collected on the prevalence of different rheumatologic ailments and complaints, and also, but for quite other reasons, on the use of oral contraceptives. Despite its size, it yielded only a few cases of rheumatoid arthritis in young women. Still, it could be an important source of information concerning the validity of the choice of the control diagnoses in our case-control design.

In view of all these possibilities, we decided, after some preliminary analyses of the EPOZ-tape, to start a case-control study.

I.2 Aim of the investigation

The aim of the research project described in the following pages was to investigate whether the halving of the incidence of rheumatoid arthritis among oral-contraceptive users relative to never-users, as originally described in a follow-up study in Great Britain, would also be demonstrable in a case-control study in the Netherlands.

I.3 Structure of the report

Chapter II contains a further elaboration of the reasons for starting the investigation. In Chapter III the theoretical basis of the case-control investigation is described in detail, while the translation of theory in practice is discussed in Chapter IV. Chapter V presents the results. In Chapter VI the findings are discussed in terms of both the present study and the future. In Chapter VII the study is evaluated in retrospect: what would we do differently if we were to start again.

CHAPTER II
REASONS FOR STARTING THE INVESTIGATION

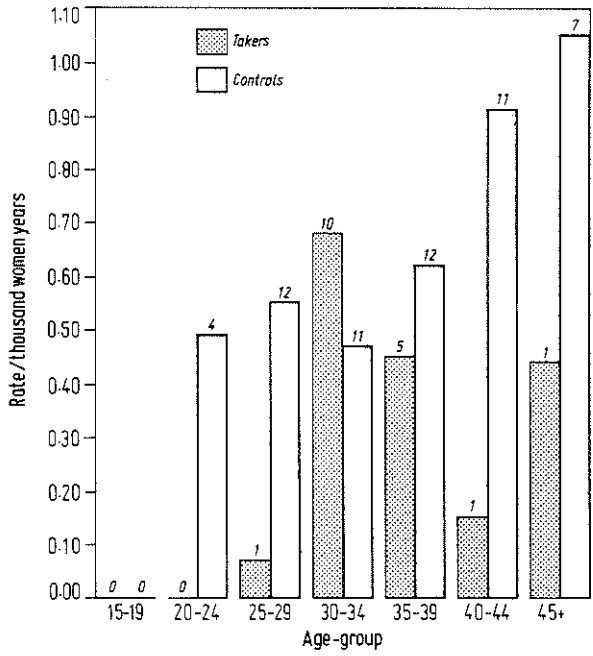
II.1 Literature on the problem

The literature on the association between the use of female hormones and the occurrence of rheumatoid arthritis consists of one follow-up study, one secular trend study, one prevalence study, some case histories, some reports on rheumatoid factor and finally, two reviews.

In 1966 the Royal College of General Practitioners of Great Britain decided to mount a giant follow-up study on oral contraceptives. Its aims were stated as: "The problem with the pill has been to determine whether the risk outweighs the benefits" (Interim Report 1974). About 1400 General Practitioners (GP) participated. They enrolled in the study women who consulted them between May 1968 and August 1969. Women who were prescribed the pill were categorised as current pill users. When stopping the pill, the women joined the category of ex-users. Each time an index person (a pill user) was entered into the study, the GP also entered a control patient, who was matched for age and marital status and had never taken oral contraceptives. The number of person-years of follow-up was counted in each of the three categories: takers, ex-takers and never-users. In the course of the follow-up, all new diagnoses were reported twice yearly. A negative association between current pill use and the occurrence of rheumatoid arthritis was first mentioned in the Interim Report in 1974. The main report on this association appeared in 1978 (Wingrave and Kay 1978). At that time, about 50,000 women had been registered, totalling close to 200,000 women-years: 60,607 women-years among the current-users, 36,008 among the ex-users and 100,047 among never-users. A total of 94 reasonably definite cases of rheumatoid arthritis occurred in the course of the follow-up. The diagnoses were reviewed by asking the general practitioner whether further specialist confirmation of the diagnosis had been obtained. The incidence rates for rheumatoid arthritis were standardized by the indirect method for age, parity, cigarette consumption and social class. The

FIGURE II.1

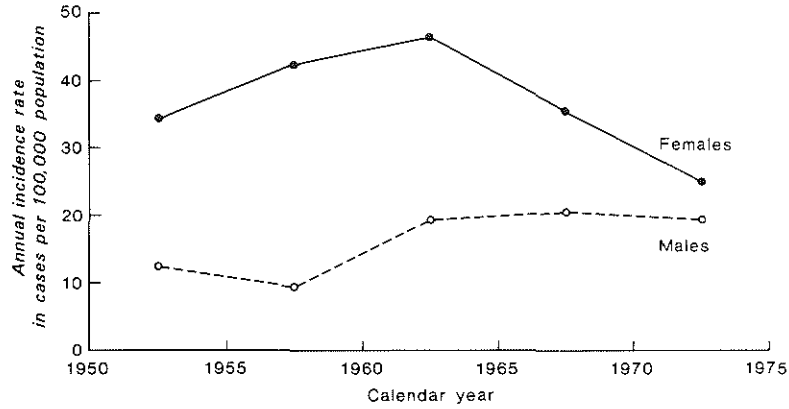
Reproduced from Wingrave and Kay (1978), with kind permission of the authors and the editors of The Lancet.



Comparison of incidence of rheumatoid arthritis in oral-contraceptive users and controls, by age at the time of diagnosis.
The number of episodes reported is shown above each column.

FIGURE II.2

Reproduced from Linos et al. (1980), with kind permission of the authors and the editors of the American Journal of Epidemiology.



Incidence rate of definite rheumatoid arthritis (RA) in Rochester, Minnesota, 1950–1974, based on initial diagnoses of RA, age-adjusted to the 1960 US total white population.

standardized incidence rate for current-users was 0.31 per 1,000 women-years, for ex-users it was 0.53/1000 w-yrs and for never-users 0.63/1000 w-yrs. The report concluded that a halving of the incidence of rheumatoid arthritis was found among current oral-contraceptive users. Some of the observations, however, should be approached with reservation. Firstly, there is the lack of some carry-over effect in ex-users. Secondly, the age distribution of the rheumatoid arthritis incidence rates is contrary to that expected for the current-users. In this category, the incidence almost drops with increasing age. See Fig.II.1. The phenomenon is puzzling, unless it is hypothesized that the older women have taken the pill for a longer time – amounting to a dose-response relationship. One cannot help but wonder whether some bias was present. Could it be that women with proven fertility, i.e. those who will use the pill more often in their forties, are less likely to develope rheumatoid arthritis? Or could it be that at the first sign of arthritis women stop taking the pill? Or that women who remain sexually active are a selection of those without musculo-skeletal aches and pains? One can only speculate about the reasons for an incidence pattern that is so different from expectation.

The second paper that suggested the possibility of a negative association between oestrogen use and rheumatoid arthritis is one describing the secular trend of rheumatoid arthritis in Rochester, Minnesota (Linos et al. 1980). The secular trends of various diseases are monitored by the diagnostic disease registry of the Mayo Clinics and other general hospitals in the Rochester area. The setting of this registry and its functioning are described by Kurland et al. (1981). All cases of probable or definite rheumatoid arthritis, encountered between 1950 and 1974 in one of the participating out- or inpatient centers, were registered. Person-years of observation were calculated from the population registries of Rochester. After direct standardization for age, the incidence of rheumatoid arthritis was shown graphically to have been declining in women since about 1960, while it remained stable, or had even increased in men. See Fig.II.2.

The idea that a disease in women has undergone a change in incidence since the beginning of the 1960s, evokes the possibility of an association with the use of some form of artificial female hormone. As a basis for their suspicion of a negative association between exogenous female hormones and rheumatoid arthritis, the authors quote the Royal College's study described in the preceding paragraph. Although the evidence from the Mayo Clinics is appealing, this secular trend can only be regarded as complementary evidence, if only because it is impossible to determine what kind of female hormone, if any, plays a role in this secular trend.

Furthermore, the clinical and epidemiological insights into what is rheumatoid arthritis and what is not, have evolved greatly since the 1950s. Since women are the group at greatest risk, they might show the largest effects of a change in clinical views. The authors state that all cases were classified according to the American Rheumatism Association's criteria following a review of the medical records. However, the criteria were published by Ropes et al. in 1957, thus just before the drop in rheumatoid arthritis incidence noted in the Mayo's registry. One wonders how even the most scrupulous of investigators can undo the effects of different diagnostic labelling in medical records of the past. Finally, Fig II.2 also suggests a decreasing sex ratio for the disease, away from the generally accepted female to male ratio of 2:1 (Hochberg 1981). A declining sex ratio would probably have come to the attention of other investigators or clinicians, but it has not. On the contrary, in a large prevalence study carried out between 1975 and 1978 in the Netherlands, the overall sex ratio was still 2:1 (EPOZ-study: Valkenburg, personal communication).

A prevalence study on rheumatoid arthritis among pill users was started in 1964 in Washington, D.C., with the aim of providing practising physicians with some background information when the pill was to be prescribed to a woman with rheumatoid arthritis or when rheumatoid arthritis developed during pill use (Gill 1968). The study was started in a planned parenthood association clinic that served a predominantly black population (92 per cent of pill-takers in the clinic were black). The prevalence of rheumatoid arthritis was said to be extremely low: 20 in 3014, or 0.7 per cent. The use of the pill did not seem to influence the course of the disease. However, the fact that this study was carried out in the early days of "the pill" and in this population in Washington, makes it likely that the subjects of this survey were highly selected. Even if only because of the uncertainties about the association of race with rheumatoid arthritis, it is difficult to interpret this prevalence figure as being higher or lower than would be expected. Furthermore, this was a population of young women who actively sought help in planning their pregnancies in the early sixties, a time when contraception was a subject of considerable debate; their age and social and educational backgrounds might be very different from those of other black women in the same area.

In 1969 a few case reports of rheumatoid arthritis developing during the use of oral contraceptives were published (Bole et al. 1969). These were followed by a casuistic report on the higher prevalence of auto-antibodies in women on the pill (Kay et al. 1971). However, in a large-scale population survey, if anything, a negative association was found between the

prevalence of rheumatoid factor and the use of oral contraceptives (Sponzilli et al. 1976). In general, such prevalence studies are difficult to interpret, since it is not known whether the rheumatoid factor was there before the pill or vice versa. In Chapter V of this report, we will present evidence that numerous women start on the pill after the (specialist) diagnosis of rheumatoid arthritis is made.

All in all, the literature is indicative for a negative association, although not entirely convincing. In his review, Hochberg (1981) summarizes the evidence of the studies mentioned in the preceding paragraphs and concludes that:"... the apparent protective effect of oral contraceptives against rheumatoid arthritis needs to be reexamined and if confirmed may lead to interesting biologic and metabolic hypotheses concerning immune response and inflammation". Likewise, Allander and Bjelle (1981) conclude that the reduction of the incidence of rheumatoid arthritis associated with the use of oral contraceptives is a specific priority of rheumatic disease epidemiology.

II.2 Public health importance

The closing remark of the paper on the follow-up study by the Royal College of General Practitioners was that the absolute effect of a halving of the incidence rate of rheumatoid arthritis is small: in one year about 1 woman out of 3000 pill takers would be protected against the development of rheumatoid arthritis. There is another view of the problem. The incidence rate of rheumatoid arthritis is indeed small – as is the incidence rate of most chronic diseases. However, rheumatoid arthritis is a disease that persists, generally for as long as the affected person lives. And even if the disease decreases life expectancy by some years, the middle-aged person who develops it will live with it for decades. These are decades of suffering, from both the disease and the cures. Moreover, because the disease tends to stay, the small incidence turns into a rather high prevalence: in adult women it is estimated to be roughly 2 per cent. If the incidence of the disease is halved by taking the pill, and if this is followed by a halving of the prevalence, then up to 1 out of every 100 pill takers could be spared many years of disablement and handicap. This knowledge could eventually influence our present-day attitude towards the risks and benefits of "the pill". How this influence might work, is discussed after the review of the results of our investigation in Chapter VI.3.

II.3 Biological interest of the hypothesis

The interest in hormones and rheumatoid arthritis is old and recurrent. In 1938 Hench first published his systematic observations that rheumatoid arthritis patients fared better during pregnancies and during periods of jaundice. Both phenomena were thought to be mediated by some aspect of hormonal metabolism. Hench indicated that the beneficial effect of pregnancy had already been described by Moore in 1864. After it had been described that plasma corticosteroid levels rise two- to threefold during pregnancy, accompanied by a rise of the corticosteroid-binding globulin (Dixon et al. 1967), and after the isolation and introduction of corticosteroids for therapeutic purposes, it was believed that these hormones provided the clue to explain the observations (Persellin et al. 1979).

As it became apparent that the immune system plays a large part in the pathogenesis of rheumatoid arthritis, the subject of hormones and rheumatoid arthritis was placed in the larger context of hormones and immune diseases. The predisposition of women towards these diseases renewed the interest in hormones. It led to speculations about whether women have a differently reacting immune system because of their need to tolerate the massive immunologic aggression of pregnancy (Inman 1978).

Today, the idea has been launched that the pill prevents rheumatoid arthritis. If true, this provides another piece of the hormone-rheumatoid arthritis puzzle, which has to be taken into account in any explanation of the causation of the disease. This then justifies the need for further epidemiologic study. The implications of the results of our investigation for further research in rheumatoid arthritis will be discussed in Chapter VI.2.

II.4 The presence of a rheumatologic registry

In clinical epidemiology, i.e. the study of functions of disease occurrence in patients (Miettinen, personal communication), diseases that are treated mainly on an outpatient basis often present problems of logistics. A minimum demand for an efficient start of a clinical epidemiologic study, such as a case-control study, is the existence of a "sampling frame". In a "sampling frame" an investigator can select those cases of a given disease occurring in a specific age and sex category. Likewise, a possible group of controls can be selected. Such a "sampling frame" can be the same as the diagnostic registry of inpatients that is commonly maintained in hospitals. This type of registration, however, is

generally not kept by outpatient clinics. Maybe this is due to the fact that most outpatient consultations are brief, involving mainly some symptomatic treatment and often not a diagnosis which is easily classifiable. Rheumatology is a clinical speciality carried out mainly in the outpatient clinic. Seemingly as a consequence, uniform diagnostic registration is rare.

In 1978 a diagnostic rheumatology registry was set up in the Netherlands, on the initiative of the Commission of Research on Rheumatic Diseases of the Council for Health Research of the Netherlands Organisation of Applied Research (TNO). The primary aim was the study of the distribution of rheumatic diseases. Participating rheumatologists were asked to complete a standard diagnostic form for each patient seen at least once during a year. The information collected was: outpatient clinic, treating physician, age, sex, date of entry in the registry, identification number (administrative or patient record), and rheumatologic diagnoses. The central computer facilities of the registry were located at the Institute of Epidemiology of the Erasmus University of Rotterdam. In 1978, when the undertaking was funded by the Netherlands Prevention Fund, thirteen rheumatology clinics participated, and a total of 13,000 patients was registered. Most of the larger clinics and academic institutions were included. In 1979 the costs had to be paid by the clinics themselves, and only six centers continued with the registration. Their reason for participation was mainly the opportunity to have a good diagnostic registry of their own patients for scientific purposes. Such a registry provides the epidemiologist with a "sampling frame" to start a case-control study. Five of the six centers that participated in both 1978 and 1979 also participated in the investigation described in this thesis.

CHAPTER III
THE THEORETICAL CONSTRUCT OF THE INVESTIGATION

III.1 The proposed outline of the investigation

The investigation was to be conducted as a case-control study. Cases and controls would be drawn from the patients registered in the diagnostic rheumatology registry which covered several of the larger outpatient clinics in the Netherlands and which was kept at the Institute of Epidemiology of the Erasmus University. Cases were to be young women (i.e. women who in 1980 were approximately 25 to 54 years old) with a diagnosis of seropositive or seronegative rheumatoid arthritis, labelled as possible, probable or definite (including "classical") according to the American Rheumatism Association criteria (the "possibles" could later be discarded in the analysis). Controls were to be women of the same age with a diagnosis of soft tissue rheumatism and/or primary osteoarthritis. Cases and controls were to be approached by their attending physicians with the same mailed questionnaire, accompanied by the same covering letter and a return envelope addressed to the Institute of Epidemiology. The questionnaire would elicit information about calendar times of GP consultations and specialist referral for rheumatic complaints, periods of pill use and reasons for use or non-use of oral contraceptives, as well as information about likely confounders (e.g. menopausal status). The covering letter would refer to the scientific and social need to know more about rheumatism and hormones in general, without revealing the hypothesis under study. The questionnaires which were returned to the Institute of Epidemiology

(eventually after a reminder) would be computerised and analysed in that institute.

The questionnaire data would be used to determine for each individual whether there had been any pill use before or during the time that medical attention for the rheumatic complaints was first sought. Comparison between cases and controls of the frequency of pill use before or during the onset of the rheumatic history would yield the necessary odds ratios.

III.2 A DISCUSSION OF THE MAIN FEATURES OF THE DESIGN OF THE INVESTIGATION

III.2.1 *The case-control design*

In our judgement the best design for an investigation into the negative association between the pill and the onset of rheumatoid arthritis would be a case-control study, because it seemed unlikely that anyone would ever fund a follow-up study to investigate this association. Even the giant follow-up study by the Royal College of General Practitioners yielded only some 94 cases of rheumatoid arthritis. In order to confirm or refute the halving of the incidence rate found in that study, an even larger series is required. Who would invest that much effort in a "chance" finding concerning a "non-killing" disease? A case-control design could be a suitable alternative. Even if rheumatoid arthritis in young women is rare, bringing together the cases known in several rheumatology clinics in the Netherlands should easily yield hundreds of patients. As "the pill" is frequently used by young women, statistical power to corroborate or refute the halving of the incidence would be high. In addition, the case-control design would be cheap – i.e. costing only the amount of money that one would want to invest in order to rule out a "chance" finding.

The case-control design is the natural extension of the taking of the medical history by the clinician. It is natural that a clinician inquires into the patient's antecedents and notes the unusual. The unusual is that which one would not expect to find in a group of people who do not have the disease. More formally, the case-control design involves a comparison between a group of patients with the disease (the cases) and a group of controls. While the first descriptions of comparisons between cases and controls date from more than a century ago, the first major successes in the epidemiology of chronic disease came in the late 1940s with the quantification of the association between lung cancer and cigarette

smoking (Lilienfeld and Lilienfeld 1979). Major breakthroughs in understanding the methodology involved were the papers by Cornfield (1951) and by Mantel and Haenszel (1959). Over the past decade, the case-control study has prospered due to both methodologic innovations and its applicability to a wide variety of diseases and exposures (Cole 1979).

The logic of a case-control design can be understood as being the inverse of that of a follow-up study. In a follow-up study, one starts with the exposure, i.e. one defines a group of exposed and a group of non-exposed persons (in this case: women-on-the-pill and women-not-on-the-pill). Both groups are followed over time, and one counts the number of cases of rheumatoid arthritis that develop in each group. The comparison of the rates of disease occurrence gives us an insight into the association of the disease with either taking or non-taking of the pill. The case-control design works inversely. The reasoning is: if it is true that in a follow-up study there will be less rheumatoid arthritis among pill users, then one expects that among a group of women with rheumatoid arthritis (the cases) there will be less pill users than among a group of women who do not have the disease (the controls). Furthermore, the ratio of the disease incidence rates, i.e. the rate-ratio, can be calculated from a case-control as well as from a follow-up study.

This important idea, i.e. that the ratio of the incidence rates of a disease is estimable from a case-control study as well as from a follow-up study, was originally developed by Cornfield (1951), expanded by Miettinen (1976) and recently refined by Greenland and Thomas (1982). While the exact derivation necessitates the use of calculus, the approximate mathematical relationships can be understood along the lines that follow. Suppose that one mounts a follow-up study of a number of **Z** women on the pill who are followed for a period of time, **t**. The amount of women-time of follow-up (e.g. women-years of pill-taking) would be **Z** times **t**. Suppose further that during the follow-up rheumatoid arthritis would develop in a number of women on the pill, called **A**. The incidence rate among pill takers becomes **A/Z.t**. Suppose that we also follow a number of women, **Y**, who are not on the pill, for a similar period **t**. The amount of women-time for the non-takers then becomes **Y.t**. If a number of women not on the pill, **B**, develop rheumatoid arthritis during the follow-up, the incidence rate of rheumatoid arthritis among non-takers becomes: **B/Y.t.** The ratio of these two incidence rates is: **(A/Z.t)/(B/Y.t).** These relationships are shown in Table III.1A.

The rate-ratio can be rewritten as **(A/B)/(Z.t/Y.t),** and now consists of a numerator **A/B** and a denominator **Z.t/Y.t.** The numerator **A/B** equals

TABLE III.1A
Follow-up study

			Incidence rate	Rate-ratio
Exposed:	Women on the pill	$Z \xrightarrow{t} A$	**A/Z.t**	**(A/Z.t)/(B/Y.t)**
Not Exposed:	Women *not* on the pill	$Y \xrightarrow{t} B$	**B/Y.t**	

the odds of exposure (pill use) among the cases of rheumatoid arthritis which newly developed during the follow-up.

The word "odds" derives from the jargon of horse and dog racing. Technically, it is the quotient of the probability that a horse will win and the probability that the horse will not. If **(A + B)** cases are present, the probability of exposure, i.e. pill use, among the cases is **A/(A + B)**. The probability of non-exposure is **B/(A + B)**. The odds of exposure becomes **(A/(A + B))/(B/(A + B))**, which simplifies to **A/B** .

The numerator of the rate-ratio was **Z.t/Y.t** . This is the ratio of the amount of population-time of follow-up among the exposed to that among the non-exposed. If follow-up time is taken to be equal and if both populations are dynamic populations in approximate steady state, then the ratio of the two amounts of population-time equals the ratio of the number of people that are in follow-up at any given moment. Thus, **Z.t/Y.t** simplifies to **Z/Y**, where **Z/Y** is the odds of exposure among the source population from which the cases derive. In consequence, the rate-ratio can be estimated by **(A/B)/(Z/Y)** , which is a ratio of two exposure odds.

However, this exposure odds ratio can also be estimated without actually doing a follow-up. This is what happens in a case-control study. There, one samples a number of cases of the disease in question, say a total

of m_1 cases, from a number of medical practices. Among these cases, there will be **a** persons who have been exposed in the past (i.e. who have been pill users), and **b** persons who have not. These m_1 cases are presumed to have arisen from the catchment population of these medical practices. The next information that one then needs to know is what the exposure frequencies are for that source population. Therefore, one proceeds to select m_0 control persons: persons who do not have the disease and can be assumed to reflect the catchment population as far as the frequency of exposure is concerned. Among the m_0 controls, there will be **z** exposed and **y** non-exposed persons. From the cases one can calculate the exposure odds, **a/b** , and likewise one calculates the exposure odds among the controls, **z/y** . The exposure odds ratio **(a/b)/(z/y)** will now be equal to the quantity **(A/B)/(Z/Y)** which was derived above, except for sampling fluctuations. As the latter ratio was equal to the rate-ratio of disease frequency, it follows that this rate-ratio can be estimated from a case-control study. The design of such a case-control study is presented in Table III.1B.

That the power of a case-control study is often higher than that of a follow-up study, given a certain amount of time and money which can be invested, can be shown intuitively. To obtain a few dozen cases of a rare disease in a follow-up study, it is necessary to follow a very large number of people. In contrast, in a case-control study, one can sample the cases where they have been collected administratively, such as discharge registrations or outpatient records. By such means, one can easily sample hundreds of cases of a moderately rare disease. The higher statistical power of a case-control study can also be shown by calculation (Rothman and Boice 1979). If in a follow-up study one would like to demonstrate a rate-ratio of one-half at a significance level of 0.05 or less, and if among the non-exposed (i.e. the non-users) the incidence of the disease is 0.5/1000 w-yrs (as is that for rheumatoid arthritis in young women), then to obtain a statistical power of 95 per cent, one would have to enroll 15,000 exposed and 15,000 non-exposed women and follow all of these women for about 10 years, yielding a total follow-up of 300,000 women-years. In contrast, if in a case-control study one would like to demonstrate an odds ratio of one-half at the same level of significance, and if the percentage exposed among the non-cases is close to 50 per cent (as it is in the general population for ever-use of the pill), then to obtain the same statistical power one only needs about 250 cases and 250 controls.

TABLE III.1B
Case-control study

	Cases	Controls
Exposed (i.e. "on the pill")	**a**	**z**
Not exposed (i.e. "not on the pill")	**b**	**y**
	m_1	m_0
Exposure odds	**a/b**	**z/y**
Exposure odds ratio		**(a/b)/(z/y)**

The exposure odds ratio can also be written as **a.y/z.b** ; it is then often referred to as the cross-product ratio.

III.2.2 *The use of prevalent plus incident cases*

In selecting our cases of rheumatoid arthritis from the diagnostic rheumatology registry which is maintained in the Netherlands (see Chapter II.4), we chose to enroll both incident and prevalent cases of the disease. Thus we included women who first consulted the physician because of rheumatoid arthritis in 1978 or 1979 as well as women who only came for a control visit in one of these years. This choice was guided by two practical considerations. Firstly, the use of both incident and prevalent cases of the disease would greatly increase the number of subjects available for study.

Since our aim was to confirm or refute an earlier finding, it was important to have a large enough series to obtain very high statistical power. Secondly, in the diagnostic rheumatology registry, we could not discern the prevalent from the incident cases. We could of course have gone back to the clinical rheumatologists for more data on all patients to identify the more or less incident ones. This would have cost additional time (and thus money). Moreover, we questioned whether one could define an "incident" case of rheumatism: most patients who come to an outpatient clinic will already have been treated by their GPs and by other specialists as well.

Finally, we considered the impact, if any, of using these prevalent cases. From a statistical point of view, prevalent cases can provide an estimate of an odds ratio (i.e. the prevalence odds ratio) which can be a good approximation, or even – under some conditions – an exact estimation of the rate-ratio (Miettinen 1976). Since rheumatoid arthritis is by and large a non-killing disease – certainly among the young – the prevalent cases would not be biased as far as factors associated with their survival are concerned. At any rate, in the analysis, we could always stratify both cases and controls according to the year of diagnosis. However, as will be explained later, we had not fully anticipated one important drawback: the inaccuracy of recall (See Chapter VI.1.3 and VII.1.2).

III.2.3 *The choice of the control group and its validity*

A major decision, when mounting a case-control study, is the choice of the control group, i.e. the group which has to yield the "expected" odds of exposure ("expected" under the assumption that there is no association between the exposure and the disease, which is the null-hypothesis). In other words, the control group should reflect the exposure pattern for the population out of which the cases arise. The main choices in this field are: population controls, either from census lists or living in the same neighbourhood as the cases, or a clinical control series, consisting of patients with other diseases. We chose controls who attended the same outpatient clinics as the cases, and who had a diagnosis of soft tissue rheumatism and/or primary osteoarthritis. This particular control group offered us first of all the usual advantages of "hospital controls", ready availability and ready cooperation, plus the inherent fact that they are drawn from the same hospital catchment population. In addition, the wide variety of diseases covered by these two diagnostic categories – a variation in kind, severity and duration – was considered to be a guarantee against other unknown associations of these control diagnoses with oral

contraceptives (Jick and Vessey 1978). The most important factor, however,was that this control series permitted us to elicit the information we wanted "blindly". Since the controls were also women with rheumatic complaints, we could approach them in exactly the same way as the cases – inquiring about the dates of onset of rheumatism and dates of pill use, and informing them that we were interested in "rheumatism" and "the pill", but not revealing the final hypothesis under study. Even if some bias were to occur because of the wording of the covering letter, i.e. more pill-takers responding, it should be the same for cases and controls.

During the preparation of the study, we were in the fortunate position of being able to check the validity of the choice of the control series in another setting. We could compare the frequency of pill use among women suffering from some of the more common soft tissue rheumatisms and/or osteoarthritis with that found for the general population free of such diseases. This could be achieved by analysing the data of the EPOZ study. As mentioned in Chapter I, EPOZ is a Dutch acronym that stands for Epidemiologic Preventive Investigation Zoetermeer. It designates a population survey that was undertaken between 1975 and 1978 in the Dutch town of Zoetermeer, a suburb near The Hague. The purpose of the survey was to determine the prevalence of several chronic diseases and their determinants in an open population. Out of a total of 13,462 inhabitants (age: five years old and over) of two of the town's districts, 10,532 participated. The overall response rate was 78 per cent. In this survey, the prevalence of clinical rheumatic conditions was ascertained. The diagnoses were made by standardised history taking, complete physical examination, X-ray examination of hands, feet and cervical spine (in those over 20 years of age), and determination of rheumatoid factor in serum. In another part of the survey which was directed toward determining the prevalence of lower urinary tract infections, questions had been asked about menses, oral-contraceptive use and the menopause. These items had not been linked previously, as the present hypothesis was not yet known at the time.

By linking of these two parts of the survey we could perform pseudo-case-control analyses, in which we could compare oral-contraceptive use between women with one of the more frequent clinical rheumatic diagnoses and women without such diagnoses. The diagnoses were: cervical spondylosis and spondylarthrosis, painful shoulder (tenosynovitis), tennis elbow, low back pain (sciatica and hernia), localised osteoarthritis and generalised osteoarthritis (three or more joint groups affected). The analysis was restricted to two age groups, 35-44 and 45-54 years old, and stratified for menopausal status. The tabulation of pill

use according to the presence or absence of the rheumatic condition, age and menopausal status is shown in Tables III.2 to III.7. For each condition an exposure odds ratio was calculated over the four age and menopausal strata by means of the Mantel-Haenszel procedure (1959). This procedure yields an overall odds ratio, roughly weighed according to the amount of information present in the strata. The 95 per cent confidence limits of the Mantel-Haenszel odds ratio were calculated by Miettinen's test-based method (1976). A short interpretation of these statistics is given in the beginning of Chapter V.4.

The odds ratios of current pill use ranged for the diverse musculo-skeletal ailments between 0.68 and 1.41, and the 95 per cent confidence intervals always included unity. We concluded that in the open population there was no association between pill use and these forms of soft tissue rheumatism or osteoarthritis. Although this is not a complete safeguard against associations between the pill and the condition as it presents itself to a rheumatologist after the selective referral by the GP, we were greatly reassured that our choice of this clinical series of controls was suitable for our case-control study.

III.2.4 *Why a mailed questionnaire?*

The use of a mailed, and thus self-administered, questionnaire to elicit the necessary information from cases and controls presented several advantages.

First, it enabled to approach cases and controls in exactly the same way, which supported our effort to "blind" both as to the hypothesis under investigation. Second, it excluded observer bias since there was no interviewer. Third, it was cheap and quick. Fourth, it was expected to be valid: we expected both cases and controls to respond in sufficient numbers, since they would be approached by their attending rheumatologist.

III.2.5 *The mailing procedure*

The questionnaire, the covering letter and a return envelope were to be mailed to the patient by the attending physician. This meant that the covering letters had to have different letterheads and be signed by different persons, depending upon the clinic. Likewise the envelopes had to show the address of the outpatient clinic. The questionnaire carried no letterhead; the return envelope was addressed to Professor Dr. H.A. Valkenburg, and carried the letterhead of the Erasmus University. All of the mail was

TABLE III.2

Use of oral contraceptives (OC) according to age, menopausal status and presence or absence of cervical spondylosis or spondylarthrosis ; EPOZ study

	Age	35-44		45-54	
		Cervical spond.		Cervical spond.	
		Present	Absent	Present	Absent
pre-menopausal	Ever OC	81	344	36	97
	Never OC	44	251	37	134
post-menopausal	Ever OC	14	46	28	60
	Never OC	11	21	68	180

Mantel-Haenszel Odds Ratio: 1.23
95 per cent confidence limits: 0.95-1.61

TABLE III.3

Use of oral contraceptives (OC) according to age, menopausal status and presence or absence of painful shoulder (tenosynovitis) ; EPOZ study

	Age	35-44		45-54	
		Tenosynovitis		Tenosynovitis	
		Present	Absent	Present	Absent
pre-menopausal	Ever OC	35	392	14	120
	Never OC	18	275	21	150
post-menopausal	Ever OC	5	54	20	68
	Never OC	1	31	36	214

Mantel-Haenszel Odds Ratio: 1.34
95 per cent confidence limits: 0.94-1.93

TABLE III.4

Use of oral contraceptives (OC) according to age, menopausal status and presence or absence of "tennis-elbow" ; EPOZ study

	Age	35-44		45-54	
		Tennis Elbow		Tennis Elbow	
		Present	Absent	Present	Absent
pre-menopausal	Ever OC	21	406	5	129
	Never OC	7	290	11	160
post-menopausal	Ever OC	2	58	7	81
	Never OC	1	31	14	236

Mantel-Haenszel Odds Ratio: 1.32
95 per cent confidence limits: 0.79-2.19

TABLE III.5

Use of oral contraceptives (OC) according to age, menopausal status and presence or absence of low back pain (hernia, sciatica) ; EPOZ study

	Age	35-44		45-54	
		Low back pain		Low back pain	
		Present	Absent	Present	Absent
pre-menopausal	Ever OC	33	394	20	124
	Never OC	18	279	14	157
post-menopausal	Ever OC	8	52	17	71
	Never OC	3	29	25	225

Mantel-Haenszel Odds Ratio: 1.41
95 per cent confidence limits: 0.97-2.09

TABLE III.6

Use of oral contraceptives (OC) according to age, menopausal status and presence or absence of Localised Osteoarthritis (up to two joints affected) ; EPOZ study

	Age	35-44		45-54	
		L.O.A.		L.O.A.	
		Present	Absent	Present	Absent
pre-menopausal	Ever OC	77	350	37	97
	Never OC	49	248	48	123
post-menopausal	Ever OC	8	52	28	60
	Never OC	4	28	92	158

Mantel-Haenszel Odds Ratio: 0.99
95 per cent confidence limits: 0.76-1.28

TABLE III.7

Use of oral contraceptives (OC) according to age, menopausal status and presence or absence of Generalised Osteoarthritis (three or more joints affected) ; EPOZ study

	Age	35-44		45-54	
		G.O.A.		G.O.A.	
		Present	Absent	Present	Absent
pre-menopausal	Ever OC	14	413	13	121
	Never OC	13	284	27	144
post-menopausal	Ever OC	4	56	15	73
	Never OC	4	28	52	198

Mantel-Haenszel Odds Ratio: 0.68
95 per cent confidence limits: 0.46-1.0

prepared at the Institute of Epidemiology of the Erasmus University. We hoped that this rather elaborate procedure would minimise the dangers of breaching professional confidence, which was guaranteed in the covering letter. It was feared by the rheumatologists that it would be rather awkward for an individual woman who had visited the physician for some vague rheumatic complaint some years ago to suddenly receive a questionnaire from an institute with an unintelligible name (e-p-i-d-e-m-i-o-l-o-g-y) in Rotterdam, inquiring into her mode of contraception. Therefore, the rheumatologists preferred to approach the patients themselves. In this study all patients were asked by their treating physician to participate in a "questionnaire survey", and to mail the completed questionnaire to a third party. It was clearly indicated in the covering letter that the aims of this enterprise were purely scientific (see Appendix A and B). Thus, the patients were totally informed by their treating physicians and could decide for themselves whether they wished to participate or not.

III.2.6 *The information requested in the questionnaire*

Our interest was whether a particular woman – case or control – had used the pill up to the moment of, or at the time of, her initial rheumatic symptoms. It would obviously be too leading to state the question in this way. In addition, there was the problem of defining the exact time of onset of rheumatism in an individual.

To tackle both problems, i.e. try not to pose leading questions and try to decide somehow when somebody is rheumatic, we decided to use the "first medical contact" as a proxy for the date of onset of rheumatism. Consequently, we were interested in pill use before or at the time of the first medical contact. In the Netherlands, the first contact for a disease such as rheumatism is nearly always with the General Practitioner (GP). After varying amounts of time, the GP might well refer the patient to a specialist. The latter, if a rheumatologist, was the source of our patient material. We thought that it was rather demanding to expect patients to remember the date of their first GP consultation for rheumatism, but they might have a good guess about the length of time before they were referred to the specialist (number of weeks, months or years). This became the first question of the questionnaire (see Appendices C and D). In contrast, patients might well remember the month and the year that they were referred to the specialist. If not recalling the date, they might find that they can easily look it up, if only on a bill or an hospital appointment card. So, a second question was the month and year of the first specialist consultation.

In between these two main questions, we included a stylized drawing of a man, on which the patients could indicate the site of their first rheumatic complaints. This drawing was used for other surveys (the previously described EPOZ study), but served here only as a memory refresher. After these initial questions about rheumatism, we asked about the menopause. Clearly, if menopausal, women would no longer use the pill – although they might use other oestrogens. A difference in menopausal status between cases and controls could be accompanied by a difference in oral-contraceptive use which has nothing to do with rheumatoid arthritis. Menopausal status might be a confounding factor (see Chapter V.3). In this part of the questionnaire, we also asked about the age when menopause occurred and how menopause occurred: surgical, medical or natural. The latter information could be used to check eventual differences or likenesses between cases and controls. Next came the questions about the pill. First, had the pill ever been used, and if so, why: avoidance of pregnancy, irregular cycles, painful periods or otherwise. The latter information was collected for use in the event that the study showed an association. Indeed, if an association were to be found, the next question would be whether cases and controls were the same type of women as far as pill use is concerned. Maybe the controls with their "softer" diagnoses (i.e. soft tissue rheumatism) are women with a higher complaint rate and a higher degree of medicalisation in general. Such women might use the pill more often for purposes other than contraception. If so, this might require a correction in the analysis. On the other hand, if there was an association and if the reasons for pill use were the same for cases and controls, this would only strengthen our belief in the association. Finally, at the end of the three-page questionnaire came the question about the periods (dates) of uninterrupted pill use. The wording of this question was taken from the mailed questionnaire designed by Rosenberg, Hennekens, Rosner et al. (1980). The combination of the answers to these questions would enable us to calculate whether a particular woman had used the pill prior to, or at the time of, the first GP visit or specialist referral. Likewise, we could calculate whether she was menopausal at that time.

Several questions were not asked in this questionnaire. First, marital status and age were not requested because these were known from the patient files. Second, we did not inquire into type of oral contraceptives and other eventual oestrogens used, nor about pregnancies and the number of children. We did not inquire into any of these since the original description of the association concerned pill use in general – and not particular brands and/or other oestrogens. Since our main aim was to confirm or refute the

original finding, we wanted to keep our questionnaire as short as possible in the hope that this would have a positive effect on the number of returns, the quality of the answers and a speedy interpretation of the results. We decided that all questions not addressed in this questionnaire were better left to later studies, after the basic association had been confirmed. See Chapters VI and VII for further discussion.

III.2.7 *The covering letter accompanying the questionnaire*

The covering letter is a very important practical part of any epidemiologic investigation conducted by mail: it determines the response rate and the possibilities for bias.

A lively account of a professional marketer's experience with mailed questionnaires and covering letters can be found in the book "Professional Mail Surveys" by Erdos (1970). Noteworthy is that in the introduction to this book it is stated that an 80 per cent or higher response rate is a reasonable goal in most circumstances.

The following statements about the art of writing covering letters have been compiled mainly from the word-of-mouth teaching at the Institute of Epidemiology of the Erasmus University, Rotterdam. They have not been tested systematically. Their empirical validation is that in the Netherlands this institute has almost always reached response rates around 80 per cent in disease surveys, be it mailed or otherwise.

1. The covering letter should start with something of genuine interest – preferably of emotional interest – to the subjects. The aim of the covering letter is to gain participation, not to indulge in the intellectual communication of ideas. If possible, the beginning of the letter should recall some experience that the subject will have had or will have shared with others (e.g. via the newsmedia: "On radio and T.V. you will have heard that...").

2. After the attention has been captured in the opening sentences, the aim of the investigation is described. Only then may the subject be invited to return the questionnaire (or partake in some other activity).

3. The covering letter should not begin with an intellectual statement such as "An investigation has been ongoing ...(or planned)...", or "Plans for an investigation require...", or "We want to ask your cooperation for an investigation...". Such statements are of interest to the investigator and his peers only. They reflect his or her preoccupations.

4. The letter should be completely open and honest about all intentions of the author. If blood must be drawn, this should be stated

explicitly. If the project is a scientific undertaking, rather than a service to the subjects, this too should be stated. Such information will enable the subject to decide whether he/she wants to participate, without having to rely on dry semi-legal formulas, such as "participation is on a voluntary basis" etc., which have a deterrent effect on response rates.

5. Guarantee professional medical confidentiality: the subjects should receive the guarantee that their responses will remain confidential and, if considered necessary, that they will be processed anonymously.

6. Subjects should be informed why *they* have been chosen for participation.

7. Subjects should receive clear feed-back information, and this should be promised. They deserve to get something for their efforts.

8. There should be very strong reasons for writing a covering letter of more than one page. Having to turn a page back and forth to grasp the meaning of a message is counterproductive.

9. Reminder letters should differ in tone and style from the original covering letter. Something new should be added, such as the reason for needing a complete survey (do not just stress that it is important). A second reminder should be completely different from the first. Finally, reminders should contain a new questionnaire and return envelope.

10. Letters and reminders should, if at all possible, be signed individually with a fountain pen or ballpoint pen to impress as a personal letter. More than one signature does not increase the credibility. On the contrary: it might weaken the personal character of the letter, since it is unlikely that all signers are equally interested or involved in the study. Letters should be typed individually – if necessary in an automated procedure like a text processor – and not be stencilled or printed. Feed-back to the respondent can be a printed form, although letters of thanks preferably should also be typed and personalized.

11. The wording of the covering letter creates the greatest problem. It is directed towards people of every rank or station, educational level and social status. The content has to be understood by everybody and should not deter the more highly educated because it is slick copywriter's prose. Tone and style should reflect conventional middle-class decency.

12. The basic assumption is that virtually every human being is interested in matters of health and disease, particularly when he/she might run the risk of developing the disease. The fact that people nevertheless do refuse to participate is largely the result of their fear of developing or having certain diseases. On the other hand most people do understand that medical

research plays a major role in solving the problems of the causation of diseases.

CHAPTER IV
THE ACTUAL PROCESS OF THE INVESTIGATION

How the theoretical construct of the preceding chapter worked out in practice is described in this chapter.

IV.1 PARTICIPATION OF RHEUMATOLOGY CLINICS AND PROBLEMS WITH PATIENT IDENTIFICATION

The original aim was to obtain the participation of all rheumatologic centers that had participated in both the 1978 and the 1979 registration. These can be grouped geographically:
- Amsterdam: Jan van Breemen Institute and Department of Rheumatology of the Slotervaart Hospital,
- Arnhem: Department of Rheumatology of the Arnhem Municipal Hospital,
- Enschede: Department of Rheumatology of the Stadsmaten Hospital and Department of Rheumatology of the Ziekenzorg Hospital,
- Leiden: Department of Rheumatology of the Leiden University Hospital,
- Utrecht: Department of Rheumatology of the Utrecht University Hospital.

In addition, we inquired into the possible cooperation of the Groningen University Hospital's Department of Rheumatology which had only participated in the registration in 1978.

Although there was great willingness and enthusiasm to cooperate, the undertaking met with insurmountable practical problems in Groningen and Amsterdam. In Amsterdam, there had just been a large-scale investigation into several aspects of the social life, including sexual activity, of rheumatic patients, and it was felt that these patients should not be asked

again to participate in yet another survey-like enterprise. In Groningen, the main problem was patient identification. This problem also occurred in other centers that participated and warrants a separate discussion.

In the diagnostic rheumatology registry, each patient is identified by a single number which corresponds to an hospital administration number or to a medical record number assigned by the Department of Rheumatology attended by the patient. The kind of identification varies greatly according to the hospital. In principle, however, all patients could be identified by their attending physicians, given this identification number. To check this assumption, we mailed a list of ten such numbers to each of the potential participating clinics. Identification posed no problems in any of the non-academic hospitals, but created difficulties in all of the academic centers. In Groningen, the problems seemed to be unsolvable at the time that we started this investigation: the administrative numbering of patients had been changed, and identification would require many of hours of handwork.

In the Leiden University clinic, the initial problem was quickly solved, thanks to the personal knowledge of the Leiden administrative computer system by one of the collaborators at the Institute of Epidemiology. In the Utrecht University clinic, the problem was not solved at the time, but a different solution was feasible: instead of drawing patients from the registration, we used the very complete outpatient records of the year preceding our investigation (i.e. mid-1980 to mid-1981).

We are happy to report that at the time of this writing "computerised" solutions were eventually found in both Groningen and Utrecht.

Nevertheless, after our first "screening", we remained with the following outpatient clinics, that were willing and able to participate:

- Department of Rheumatology of the Arnhem Municipal Hospital,
- Department of Rheumatology of the Stadsmaten Hospital Enschede,
- Department of Rheumatology of the Ziekenzorg Hospital Enschede,
- Department of Rheumatology of the Leiden University Hospital,
- Department of Rheumatology of the Utrecht University Hospital.

During preparations for the study it soon became clear that these five centers could provide more than enough patients from different geographical and cultural regions. Moreover, we were glad that we did not exhaust all potential participants at once, since additional investigations might be requested later in case the present investigation confirmed the association.

IV.2 A PILOT STUDY OF THE QUESTIONNAIRE

Since we had learned a great deal from "screening" the patient identification system, we also performed a small pilot study of the questionnaire. We mailed a covering letter, plus questionnaire, plus return envelope to 17 patients currently attending the Utrecht clinic. Of these, 13 responded (7 out of 9 cases and 6 out of 8 controls). The completion of the questionnaire seemed satisfactory, and all responses were usable. We believed that both these responses and the subject's performance in the completion of the questionnaire were good omens for our undertaking.

The respondents to the pilot study identified one problem of the questionnaire, however. In the original questionnaire the wording of questions 1, 2, and 3 (See Appendices C and D) referred to the "first consultation with the specialist (the rheumatologist) for these complaints.....". Several of the patients drew our attention to the fact that the first specialist they had consulted for their complaints was not a rheumatologist, but an internist, orthopedist, physiotherapist or neurologist. We changed the questionnaire accordingly.

IV.3 SELECTION OF PATIENTS AND VERIFICATION OF DIAGNOSES

In the files of the rheumatology registry we counted the number of potential cases and controls for the five clinics that finally participated. For Utrecht this was only an approximation of the real selection which was based on the 1980/81 outpatient records. Potential cases were defined as women with a diagnosis of possible, probable or definite rheumatoid arthritis, according to the American Rheumatism Association Criteria (ARA) (Ropes et al. 1957) – as well seropositive as seronegative – and who were born between 1926 and 1956; in 1980 therefore these women were 24 to 54 years old. Potential controls were women with a diagnosis of soft tissue rheumatism (bursitis, tenosynovitis, shoulder-hand syndrome, vertebral nuclear hernia, low back pain) or primary osteoarthritis (localised in knee, hip, vertebrae, or generalised) and with the same restriction for year of birth. The total number of potential cases in the registry was about 750, while the total number of potential controls was about 660. These large groups caused problems of logistics: not only the large number of questionnaires that would have to be mailed, but mainly the preparatory work of matching the identification number to names and addresses, copying these, and checking the diagnoses. The verification of the diagnosis consisted mainly of checking whether the original diagnostic category under which the patient

was entered in 1978 or 1979, was still maintained on subsequent visits. In the two academic centers, this work was carried out by the author of this thesis; in the non-academic centers, verification was performed by the rheumatologists themselves. For most of the administrative work we relied upon the good-will of the participating rheumatologists and their staff. Therefore, we decided to use just enough cases and controls to obtain adequate statistical power (i.e. around 95 per cent), and to relieve as much as possible the administrative staffs of the rheumatologists.
This resulted in the following practical decisions:
– At the Leiden University Hospital we would try to use all potential cases and controls. This involved little work, because not only the administration but also the diagnostic listings of the patients were completely computerised.
– At the Utrecht University Hospital, we would also use all potential cases and controls, since we could obtain a copy of all names, addresses, dates of birth and diagnoses of all patients who had attended the outpatient clinic in 1980-81. If the diagnosis was unclear, it was checked in the records by the author of this thesis.
– At the three other clinics, two in Enschede and one in Arnhem, we would impose a maximum number of patients for identification and verification of the diagnosis. We would use no more than 100 cases and no more than 100 controls per clinic. If more were available, we would randomly select cases and controls up to less than 100 of each. The main aim of this procedure was to relieve the burden on the non-teaching rheumatologists, all of whom had volunteered to check these diagnoses themselves, and on their secretaries who had to look up the names and addresses. Sometimes, the procedure resulted in different sampling fractions for cases and controls in one clinic. The odds ratio, however, is insensitive to this differential sampling. The random selection was performed by computer random number generation.

Our final aim was to sample about 450 cases and about 450 controls who would receive the questionnaire. We expected a response rate of 75 per cent and anticipated that some patients would have to be excluded due to concurrent major diseases (cardiovascular or cancer). All in all this would still result in about 300 cases and 300 controls available for analysis, which would satisfy our requirements regarding statistical power.

IV.4 Final enrollment, mailing and response

The identification of patients and the verification of diagnoses resulted in the loss of some potential cases and controls. Only a handful could not be identified, presumably due to some error in the identification number. The verification of the diagnoses, however, resulted in more losses. This was important in two respects. Several of the patients with "possible rheumatoid arthritis", especially those with "possible seronegative rheumatoid arthritis" had also been registered under the diagnosis of soft tissue rheumatism or osteoarthritis. This was often changed in either one direction during the review. In the end, all patients with a diagnosis of *any* rheumatoid arthritis were classified as cases and excluded from the control category. In the analysis, we later discarded the cases with a diagnosis of "possible" rheumatoid arthritis only. Another problem was that several patients, especially among the controls, had major concurrent diseases. Presumably these patients were referred from other departments (cardiology, oncology, psychiatry) for some remaining joint problem. These patients were excluded from final enrollment.

The flow of the patients from potential case or control status to actual enrollment is shown in Table IV.1. The transition between the first column of the table and the second, is due to the different selections we made for each clinic, as described in the previous section, and to the occasional double diagnostic registrations of patients. The transition from the second column to the third is due to eliminations after patient identification and verification of diagnosis, as described above.

All patients who were enrolled received the same mail parcel containing the same covering letter, the questionnaire and the return envelope. The only difference between the clinics was the letterhead on the parcel and on the covering letter, as well as the person(s) signing the letter. Examples of all of these items can be found in Appendices A to F. All parcels were prepared at the Institute of Epidemiology. All names and addresses of all patients who were finally enrolled were entered in computer files according to clinic and according to case or control status. This facilitated the printing of address labels. From each of the participating rheumatologists, we had received hundreds of envelopes with their letterhead, or that of their clinic, and hundreds of sheets of letter-headed type-writer paper. The covering letter was first typed on blank paper, then signed with black ballpoint pen by the rheumatologist and finally reproduced on the letterhead paper by off-set techniques at the printing office of the Medical Faculty. The questionnaire was also typed and

TABLE IV.1

Selection process for cases and controls, and response rates to questionnaires, according to clinic

Hospital Outpatient Clinic	Case or Control	Present in registry (1978 + 1979)-	Selected from registry[2]	Question-naires mailed[3]	Response[4]
Leiden	cases	120	119 (all)	91	73 (80.2)
University	controls	202	185 (all)	145	121 (83.4)
Utrecht[1]	cases	–	–	106	96 (90.6)
University	controls	–	–	74	61 (82.4)
Stadsmaten	cases	48	46 (all)	34	30 (88.2)
Enschede	controls	99	88 (all)	74	62 (83.8)
Municipal	cases	268	90 (1/3)	90	83 (92.2)
Arnhem	controls	184	99 (1/2)	90	76 (84.4)
Ziekenzorg	cases	112	79 (3/4)	65	53 (81.5)
Enschede	controls	85	82 (all)	82	69 (84.1)
Total	cases			386	335 (86.8)
	controls			465	389 (83.6)

[1] In Utrecht, patients were selected from 1980-81 outpatient records.
[2] Sampling fraction (random selection) in brackets: some discrepancies with previous column due to double indexing of patient.
[3] After identification, verification of diagnosis and exclusions of concurrent major diseases.
[4] Response rate in brackets, as a percentage. The few patients who could not be located due to a change of address were included as non-responders in this table.

multiplied by off-set. The return envelopes were readily available, as they are standard for epidemiologic investigations at the Institute of Epidemiology. When all of the parcels of a given center were ready for mailing, they were sent together to the rheumatologist's office for mailing as separate letters. To be able to keep track of who received which letter when, required the use of a patient identification number which was written on the questionnaire.

The response rate for the first mailing varied between the five centers from 50 to 60 per cent. About 4 to 6 weeks after the first mailing, a reminder was sent to the non-respondents by the same procedure. The reminder was a new parcel with a reminder letter, a new questionnaire and a new return envelope. The reminder differed in tone and in content from the covering letter, in order to catch the attention again. The inclusion of a new questionnaire and return envelope was done because it was thought likely that persons who do not respond to a questionnaire throw it away. In the event that they change their minds upon receiving the reminder, they should be given a real second chance. To put their consciences at ease, it was mentioned in the reminder that a new questionnaire was enclosed because it was possible that the earlier parcel "had not arrived". All mailings took place between October 1981 and April 1982.

The final response rates, after the reminder had been sent, are given in the last column of Table IV.1. The overall response rate varied between the clinics from 82.2 to 88.3 per cent. For cases it varied between 80.4 and 92.2 per cent, and for controls between 82.4 and 84.4 per cent. In view of these response rates, we judged that the response of cases and controls was uniformly high and that it was unlikely that further reminders would yield much, except poorly completed questionnaires. It was our general impression that the last responses received – the late responses after the reminder – were indeed of inferior quality.

IV.5 Coding of the information

The answers to all returned questionnaires were coded onto optical reader forms by the author. These forms permit to code data with a pencil and erase them if necessary. The information to be coded and the coding criteria can in principle be printed on the sheet, which permits its use by lay respondents. It is also possible, as was done in this investigation, to use a standard sheet for recoding of a questionnaire.

As always when coding questionnaires, some judgement by the coder is necessary. Some questionnaires were not usable at all, due to

TABLE IV.2

Correspondence between the author's and the computer algorithm's coding of exposure to oral contraceptives (OC) relative to onset of rheumatism ; all usable questionnaires of patients whose first GP contact was in 1960 or later

Author	Computer algorithm		
	No OC before first GP visit	OC started *and* ended before first GP visit	OC still taken at first GP visit
No OC before first GP visit	301	2	1
OC started and ended before first GP visit	1	105	6
OC still taken at first GP visit	2	3	137

incompleteness (see Chapter V.1). On others, the patients had volunteered extra written information which could influence the coding. These comments usually referred to the question on menopausal status, which was ambiguous in some respects (see Chapter VII.2). Finally, as already indicated in Chapter III.2.2, the use of prevalent cases of the disease resulted in recall difficulties. For example, some women indicated that the first specialist consultation was in "May or June 1967", or worse "somewhere in 1967", or still worse "in June 1967 or 1968". If two months or two years were indicated, the most recent one was coded. If no months were indicated, but only the year was given, this was coded as the middle of the year. Since this information was used to calculate whether a woman was using the pill at the onset of her rheumatism, it is obvious that some exposure misclassification will have resulted. The extent to which this influences our results is discussed in Chapter VI.1. In addition to the information present on the questionnaire, other information from the patient's record was also encoded on the optical reader forms: marital status, year of birth and diagnosis. The diagnostic categories for the cases were: seropositive or seronegative rheumatoid arthritis, each with the subcategories "possible", "probable" or "definite". For the controls, three categories were used: "soft tissue rheumatism", "osteoarthritis" and "miscellaneous" (arthralgias, various pains and aches).

The fact that all codings of the exposure were performed by the author can rise the suspicion of observer bias. Therefore, the codings of the exposure were checked by a computer algorithm which calculated whether pill use had preceded the onset of rheumatism from the following bits of information: year of birth, year of first specialist consultation, delay between GP and specialist and first date of first use of oral contraceptives. Table IV.2 gives one example of a crosstabulation of the author's coding of pill use before the onset of (GP) rheumatism versus the results of a computer algorithm.

The few discrepancies were either gross coding errors, or changes in the code resulting from additional written information volunteered by the patient, which could of course not be processed by the computer. The number of discrepancies, however, is so small that it cannot influence the results in an appreciable way. All of these discrepancies were checked for coding errors and, if necessary, decided upon by the author.

CHAPTER V
THE ANALYSIS OF THE INVESTIGATION

The first concern in this chapter is the pruning of the material: how and why it was necessary to discard several of the questionnaires from the analysis. This is followed by a discussion of the proper definition of the exposure to oral contraceptives. Next follows the description of the case and control characteristics which are potential confounders. Then, we present the actual analysis: the crude results, the adjustment by simple stratification, the adjustment by logistic modelling and, finally, some additional analyses, such as a dose-response analysis, an analysis according to subgroups and an analysis based on a different exposure definition.

V.1 THE PRUNING OF THE MATERIAL

Our first contact with the data, the 724 returned questionnaires from 335 cases and 389 controls, made it clear that several of the questionnaires could not be included in the analysis for different reasons.

Firstly, it had already become apparent during the coding procedure that some of the questionnaires had been filled in too poorly to be used. For example, crucial information about dates of pill use, date of first specialist consultation and/or GP delay was missing or unclear. This was encountered on about 10 per cent of the returned questionnaires. All of these questionnaires were removed from further analysis.

Secondly, due to our use of prevalent cases of rheumatism, a number of patients had experienced the onset of their disease before 1960, i.e. at a time when oral-contraceptive use was virtually non-existent in the Netherlands. These patients therefore could never provide any information about the association between oral-contraceptive use and rheumatism. This applied for about 15 per cent of the usable questionnaires. The questionnaires from these persons were also not subjected to further analysis.

Thirdly, for a number of patients with rheumatoid arthritis the diagnosis was only labelled as "possible". In the course of the diagnostic review, either by the author or by the attending rheumatologists, it was noted that most of the changes made concerned patients from this diagnostic category. The more secure diagnoses of "probable" or "definite" rheumatoid arthritis were rarely changed. It seemed, however, that there remained considerable overlap, especially between the diagnosis of "possible seronegative rheumatoid arthritis" and the control diagnoses of soft tissue rheumatism and/or osteoarthritis. This problem illustrates the usefulness of the probability labelling of the diagnosis of rheumatoid arthritis, which was once introduced by the American Rheumatism Association (Ropes et al. 1957) to reduce confusion and thus allow clinicians and epidemiologists to study the disease in the domain of the more secure diagnoses. Shifts between the various probability categories of rheumatoid arthritis are common experience in the rheumatological literature. It is known to be a problem particularly for the "possible" category. The latter category requires only two diagnostic criteria among the following: morning stiffness, tenderness or pain on motion (for at least three weeks), history or observation of joint swelling, and subcutaneous nodules (Currey 1978). Obviously, most of these patients will in the end receive another diagnosis. We decided not to include the "possibles", about

10 per cent of the cases, in the analysis. Of the remaining cases, 90 per cent were "definite" (including "classical") and 10 per cent "probable".

An overview of the successive amputations of the material, is given separately for cases and controls in Table V.1. All in all, 228 cases of probable or definite rheumatoid arthritis and 302 controls remained for the final analysis that is presented in the following sections. The distribution of the main diagnostic categories among the patients of the case and control groups is given in Table V.2.

The process of pruning described above may give rise to the question of whether it could have introduced bias.

The statistical power, fortunately, withstood this pruning, due to the fact that a case-control investigation involving exposure frequencies in the neighbourhood of 50 per cent, say between 20 per cent and 80 per cent, needs the least number of subjects to obtain sufficient statistical power (Crombie 1981). The exposures we were interested in, pill use categorised as current-use or ever-use, have estimated population frequencies between 20 and 50 per cent. Therefore, even 200 cases and 200 controls give a statistical power of 90 per cent or higher, when one wants to demonstrate an odds ratio of one-half at a significance level of 0.05.

It is difficult to see how the successive pruning of the material could have introduced bias. Poorly completed questionnaires might be a matter of education or inadequate attention or interest. Education might be associated with pill use, especially in the early years of the pill, but its proxy – socio-economic class – is not known to be associated with rheumatoid arthritis. Discarding the data for the women whose rheumatism started before 1960 has no influence on the analysis at all. Upon stratification according to year of onset of rheumatism, the fourfold tables representing the experience of these women would contain a row of zeros, plus a marginal zero, since neither the cases nor the controls whose disease began before 1960 will have used the pill before the development of the disease. Although it is not necessary to discard them before the analysis, since after stratification they will not contribute anything to the estimated odds ratio (they only yield multiplications with zero), we chose to do so, in order to avoid presenting an inflated case and control series which would include a certain subgroup that provides no information at all. Finally, the elimination of the uncertain diagnoses can only augment the odds ratio since it augments the contrast between the cases and the controls: the loading of the case-group with uncertain and possible non-cases would have diminished from the difference between the two groups.

TABLE V.1
Pruning of data[1]

	Responders	Usable	GP contact after 1960	Exclusion of "possibles"
Cases	335	308(91.9)	256(83.1)	228(89.1)
Controls	389	348(89.4)	302(86.7)	302(100)
Total	724	656(90.6)	558(85.1)	530(94.9)

[1] In brackets percentage of previous column.

TABLE V.2
Distribution of diagnoses among cases and control patients used in the final analysis

		Number	per cent
Cases	Seropositive RA	148	65,9
	Seronegative RA	80	35,1
	Total	228	
Controls	Soft Tissue	168	55.6
	Osteoarthritis	107	35,4
	Others[1]	27	8.9
	Total	302	

[1] Various ill-defined aches and pains; clear psychiatric syndromes were excluded.

V.2 The proper definition of exposure to oral contraceptives

The several ways in which the material could be used to tabulate the exposure frequencies presented a problem in itself.

The exposure we were interested in was the use of oral contraceptives before and/or during the onset of rheumatism. In principle, the following situations could be present in our questionnaire data:

- women never used oral contraceptives up to the date of our investigation,
- women started to use oral contraceptives before the onset of rheumatism, but also stopped using the pill before that onset,
- women started to use oral contraceptives before the onset of rheumatism, and were still on the pill at the time of onset,
- women started to use oral contraceptives only after the onset of rheumatism.

For the onset of rheumatism we could choose between two definitions:

a. the date of the first specialist consultation,

b. the approximate date of the first GP consultation, calculated from the date of the first specialist consultation and the delay between the GP and the specialist.

Crosstabulation of the four exposure categories with these two definitions of the onset of rheumatism is given separately for cases and controls in Table V.3.

The number of women who had never used oral contraceptives up to the date of answering our questionnaire was obviously independent of the definition of the onset of rheumatism. On the other hand, the number of women who had started oral contraceptives after the onset of rheumatism was much higher among cases than among controls. There was not much difference in this respect between the two definitions for the onset of rheumatism. The most troubling result was that the number of controls taking the pill at the time of the onset of rheumatism decreased between the first contact with the GP and the first contact with the specialist.

Confronted with these findings, we reasoned as follows:

1) As we were interested in the effect of oral contraceptives on the onset of rheumatism, any pill use which started after that onset would be irrelevant: it would no longer be able to prevent that onset. Furthermore, it is likely that a woman who is confronted with the diagnosis of a chronic disease will start to take the pill, which could explain the higher percentage of new pill users after the onset of the disease in the cases. An alternative explanation is that the cases are somewhat younger and contacted the physician in an earlier

TABLE V.3

Oral-contraceptive use, relative to medical contacts for rheumatism, in percentages

	General Practitioner[1] contact		Specialist contact	
	Cases	Controls	Cases	Controls
– Never[2] used OC	50.0	36.8	50.0	36.8
– OC started before, and stopped before	11.0	27.5	11.8	34.8
– OC still taken at time of	20.2	28.1	20.6	22.2
– OC started after	18.8	7.7	17.5	6.3
Total number	228	302	228	302

[1] Calculated from date of specialist consultation and GP delay.

[2] "Never" means here: to date of completion of questionnaire.

calendar year (see Table V.4A and discussion in next section), so that they have somewhat more time left to start the pill. We decided that from the point of view of preventing rheumatoid arthritis, any pill use starting after the onset of the disease should be regarded as non-use as far as the development of the disease is concerned.

2) The fact that more controls had stopped taking the pill at the time of the specialist consultation, could be due to the much longer delays between first GP consultation and first specialist consultation for the control patients. That this delay was much longer was apparent on simple inspection of the data (see Table V.4A and discussion in next section).

3) Whatever the above reasoning which is based partially on the data, our interest was in pill use around the time of onset of the disease. Thus, the earliest definition of the onset would be closest to the time of real onset, and was therefore preferable.

The consequence of this reasoning was that we focussed attention on oral-contraceptive use relative to the time of the first GP consultation. From that point of view, women who had started on the pill after this visit should be regarded as never-users. Thus, for the subsequent analyses, the following definitions were used:

– "Never"-users: no oral contraceptives used before the first GP-consultation for rheumatism.

– "Ex"-users: use of oral contraceptives started but also ended before the first GP consultation.

– "Current"-users: oral contraceptives started before and still in use at the time of the first GP consultation.

– "Ever"-users: any use of oral contraceptives started before the first GP consultation. This category is the sum of "Ex"- and "Current"-, or alternatively, the complement of "Never".

The crude results, according to this definition, are given in Table V.5 of Section V.4; to obtain these values out of Table V.3, the pill use which started only after the first GP contact was added to the category of never-use.

A drawback of this procedure is that the date of first GP consultation is only known approximately. It is calculated from the date of first specialist consultation and the time lag between the GP consultation and specialist referral, as indicated by the patient. In consequence, our categorisation of the exposure is liable to errors. The implications will be discussed in Chapter VI.1.

V.3 Basic characteristics of cases and controls: confounding and other sources of bias

In the conduct and especially the analysis of a case-control study, it is crucial to verify whether cases and controls differ in characteristics that are associated with the exposure in a way that could bias the study's results. Such characteristics are called confounding factors. The situation is somewhat analogous to the basic concern in clinical trials. In a randomized trial, the randomization procedure is adopted specifically to ensure that the

TABLE V.4A
Characteristics of 228 cases and 302 control patients, centiles

			Centiles		
			10	50	90
Year of birth	Cases[1]	Seropos RA	1927	1934	1947
		Seroneg RA	1927	1938	1949
		All	1927	1935	1948
	Controls[2]	Soft Tissue	1927	1936	1948
		Osteoarthritis	1926	1929	1940
		Others	1930	1940	1948
		All	1927	1933	1946
Year of first GP visit	Cases	Seropos RA	1963	1972	1978
		Seroneg RA	1964	1974	1978
		All	1963	1973	1978
	Controls	Soft Tissue	1970	1977	1979
		Osteoarthritis	1967	1977	1979
		Others	1967	1977	1970
		All	1968	1977	1979
Delay between GP and Specialist visit (months)	Cases	Seropos RA	0.5	3	24
		Seroneg RA	0.25	3	24
		All	0.5	3	24
	Controls	Soft Tissue	0.75	6	62
		Osteoarthritis	0.75	6	50
		Others	0.5	8	44
		All	0.75	6	50

[1] Of the cases 70 were seronegative and 148 seropositive.
[2] Of the controls 168 had soft tissue rheumatism, 107 osteoarthritis and 27 were miscellaneous.

TABLE V.4B

Characteristics of 228 cases and 302 control patients, percentages

		Married	Pre-menopausal[1]
Cases[2]	Seropos RA	82.5	95.9
	Seroneg RA	89.5	88.8
	All	86.8	93.4
Controls[3]	Soft Tissue	89.3	86.9
	Osteoarthritis	92.5	74.8
	Others	96.5	77.8
	All	91.1	81.8

[1] Calculated back to time of GP visit.

[2] Of the cases 70 were seronegative and 148 seropositive.

[3] Of the controls 168 had soft tissue rheumatism, 107 osteoarthritis and 27 miscellaneous.

exposure, e.g. the drug treatment, is not associated with any of the factors that influence the probability of the outcome (Fisher 1951). To verify that the randomization has "succeeded", it is common practice that the first table of the results of a clinical trial gives some important base-line characteristics of the exposed and the non-exposed to confirm that these groups do not differ in important determinants of the disease. In a case-control study, the situation is reversed. What is measured in a case-control study is the frequency of exposure among cases and controls. Out of this the odds ratio is calculated. This odds ratio is said to be confounded when cases and controls differ in characteristics associated with the exposure, either inherently (i.e. the characteristic is associated with another determinant of the disease; the latter determinant will always be more common in the case series) or by some differential selection process (Matroos 1981).

The subject of confounding is a much debated one (Miettinen 1981). In practice, we prefer to use the most basic definition of a confounder: a factor which influences the odds ratio so that a biased estimate results, i.e. an estimate that does not reflect the true impact of the exposure under study.

During the design of the study, we thought of several possible confounders: age, marital status, menopausal status, year of onset of rheumatism and clinic. In addition, we were concerned that the reason for pill use might differ between cases and controls. Whether this could properly be called a confounding factor is not certain – however, it can without any doubt be a source of bias.

The summary of these base-line characteristics is tabulated in Tables V.4A and V.4B.

Several differences emerge which can – in and by themselves – lead to differences in exposure frequency between cases and controls, irrespective of the presence of a real association between the pill and rheumatoid arthritis. The cases are somewhat younger than the controls. In general, the probability that a younger women uses the pill is higher, while for an older woman the probability is higher to "ever" have taken the pill. In contrast, the year of first GP visit is somewhat earlier for the cases, the median being 1973 for the cases, while it is 1977 for the controls. This could have an inverse effect: the chance of having started the pill in 1973 was certainly less than that in 1977. Presumably, the cases tend to be more chronical, requiring prolonged supervision by the rheumatologist, since they were still listed in the 1978/79 registry or in the 1980/81 outpatient records. For the cases the delay between the GP diagnosis and the first specialist consultation was much shorter, compared to that for the controls.

This is important, as it might explain some of our earlier findings about a change in the use of oral contraceptives between the time of GP consultation and the time of specialist consultation among the controls. However, in the analysis it will not influence our results since we define exposure as pill use at the time of the GP consultation: what follows thereafter is not our concern in this analysis. The cases are married less often than the controls. Despite the liberalisation of sexual mores in the Netherlands, this could tend to yield fewer cases-on-the-pill. The controls were much more frequently menopausal at the time of the first GP consultation; this could reduce the use of contraceptives among the controls.

Finally, more of the cases used the pill to avoid pregnancy: 93.7 per cent of the cases who ever used the pill before the onset of rheumatism indicated avoidance of pregnancy as one of the main reasons for use, whereas only 85.0 per cent of the controls-on-the-pill listed this reason. Again, the age and temporal differences could play a role in explaining this difference. It could also be that part of the controls were much more medicalised women, e.g. because of a higher complaint rate in general, which could lead to more frequent use of oral contraceptives because of menstrual complaints. Of equal concern is the different case-to-control ratio among the various rheumatology clinics, as shown in Table IV.1. If at the same time the use of the pill should differ between the clinics (either because of geographic association with religion, or because of selection of patients due to preference for certain physicians), this could in itself lead to biased estimates, if the results are not stratified by clinic.

All in all, several forces attract the exposure in turn to the cases and to the controls. Although it is possible that they balance each other out, it would be unwise to rely on the assumption of equal balance. Rather, we will include these factors in the analysis and study their effect upon the estimation of the odds ratio.

V.4 Definitive analysis

V.4.1 *Crude results*

V.4.1.1 A short interpretation of the statistics used in the analysis

The statistics used for the analysis of the results are the odds ratio and its 95 per cent confidence interval.

The odds ratio, as it is used here, is synonymous to the rate-ratio. The

odds ratio equals unity when there is no association between the exposure and the disease: then, the incidence rate of the disease among the exposed (the pill users) is equal to that among the non-exposed (the non-users). When the odds ratio differs from unity, the incidence rate of disease among the exposed differs from that among the non-exposed. If the odds ratio is larger than unity, the incidence rate of the disease among the exposed is that many times larger than the incidence rate among the non-exposed, and vice versa. The derivation of the odds ratio for a case-control study and its mathematical relationship with the rate-ratio were presented in Chapter III.2. An example of its calculation is given in the next section.

The 95 per cent confidence interval of the odds ratio is given as two limits: an upper 95 per cent confidence limit and a lower 95 per cent confidence limit. The 95 per cent confidence interval is the complement of the 5 per cent p-value. If unity lies outside of the 95 per cent confidence interval (either below the lower limit or above the upper limit), then the odds ratio is significantly different from unity at a p-value of 5 per cent or less. If the upper or the lower limit of the confidence interval exactly equals unity, the level of significance of the odds ratio is exactly 5 per cent. If the value unity falls inside the inverval, the odds ratio does not differ significantly from unity at the 5 per cent level. Why confidence intervals are used instead of p-values and how they were calculated, is explained in Section V.4.2.

V.4.1.2 Tables of crude results

The overall distribution of the exposure frequencies for cases and controls is given in Table V.5. The definition of the different exposure categories follows the description presented in Section V.2.

From Table V.5 we can calculate odds ratios, relative to the category of never-users. For the category of ever-users, the odds ratio becomes $((25+46)\text{x}134)/((83+85)\text{x}157) = 0.36$. Likewise, in the category of ex-users the odds ratio is $(25\text{x}134)/(83\text{x}157) = 0.26$. In the category of current-users, it becomes $(46\text{x}134)/(85\text{x}157) = 0.46$. For each of these odds ratios, the 95 per cent confidence interval was calculated. The odds ratios and their 95 per cent confidence limits are given in Table V.6.

V.4.2 *Adjustment for confounding by simple stratification*

Since the cases and the control patients differed in characteristics that influence their pill use – see Section V.3 – we ought not to compare them

TABLE V.5

Frequency of oral contraceptives exposure categories among cases and controls

Exposure category[1]	Cases	Controls
Never-users:	157(68.9%)	134(44.4%)
Ever-users:		
Ex-users	25(11.0%)	83(27.5%)
Current-users	46(20.1%)	85(28.1%)
Total	228	302

[1] Definition: see Section V.2.

TABLE V.6

Odds ratio estimates for different categories of oral-contraceptive use relative to never-use

	Never-use	Ex-use	Current-use	Ever-use
OR	1	0.26	0.46	0.36
95% conf. int.		(0.16-0.42)[1]	(0.30-0.70)	(0.25-0.52)

[1] 95 per cent confidence interval of odds ratio.

directly as was done in the previous section. Instead, we should compare like with like, e.g. cases vs. controls of the same age, same year of first GP visit, same menopausal status, etc. The simplest way to achieve this, is to stratify for such variables. This permits to calculate an odds ratio for each of these strata as well as a summary odds ratio for all strata. The latter is a kind of weighed estimate: an odds ratio which is a weighed average of the stratum-specific odds ratios. The most commonly used method for obtaining such a summary estimate is the Mantel-Haenszel odds ratio (Mantel and Haenszel 1959). This summary odds ratio is then accompanied by 95 per cent confidence limits; for this purpose we will use the test-based confidence limits, as described by Miettinen (1976).

V.4.2.1 Methods

Mantel-Haenszel odds ratio.

Imagine an overall table with cases and controls which are exposed or non-exposed, as presented in Table V.7.

TABLE V.7

	Exposed	Non-exposed	Total
Cases	**a**	**b**	
Controls	**c**	**d**	
			T

In this table, **a** , **b** , **c** and **d** denote the numbers in each cell, and **T** the total number in the study. The crude odds ratio would be calculated as **ad/bc**.

Such a table can be split according to some dichotomous characteristic into two subtables, as in Table V.8.

In this table, $\mathbf{a_1}$, $\mathbf{b_1}$, ... , $\mathbf{a_2}$, $\mathbf{b_2}$, ... denote the numbers in the cells of the strata, and $\mathbf{T_1}$, $\mathbf{T_2}$ the total numbers in each of the strata.

For each of the strata, one can calculate odds ratios: $\mathbf{a_1d_1/b_1c_1}$ and $\mathbf{a_2d_2/b_2c_2}$. These odds ratios will generally be based upon small numbers, especially if the data are stratified into more than two strata. The estimates

TABLE V.8

	Stratum 1		Stratum 2	
	Exposed	Non-exposed	Exposed	Non-exposed
Cases	a_1	b_1	a_2	b_2
Controls	c_1	d_1	c_2	d_2
		T_1		T_2

will therefore be unstable. A summary odds ratio, which is considered to be the underlying "common" value for all of these strata, can be calculated by the Mantel-Haenszel procedure (1959).

Mantel-Haenszel Odds Ratio

$$\frac{(a_1d_1/T_1) + (a_2d_2/T_2)}{(b_1c_1/T_1) + (b_2c_2/T_2)} = OR_{MH}$$

The effect of this procedure can be described intuitively as assigning weights to the stratum-specific odds ratios according to the amount of information which is present in each stratum (Miettinen, personal communication). Suppose that stratum 1 is much larger than stratum 2.

Then we expect that the product $\mathbf{a_1 d_1}$ will be the product of two relatively large numbers, which will yield an even larger number. In contrast, $\mathbf{a_2 d_2}$ is the product of two small numbers and will remain a relatively small number. This becomes clear when one imagines that, due to the smallness of stratum 2, either $\mathbf{a_2}$ or $\mathbf{d_2}$ becomes zero, or almost zero. Even after dividing $\mathbf{a_1 d_1}$ by $\mathbf{T_1}$ to correct for the total amount of information present in the stratum, the result still be much larger than the equivalent $\mathbf{a_2 d_2 / T_2}$. Again this becomes clear if one imagines that $\mathbf{a_2}$ or $\mathbf{d_2}$ equals zero. From this it follows that the numerator of the formula for OR_{MH} will be made up mainly of information from the larger stratum 1. The same will be true for the denominator. This demonstrates that the Mantel-Haenszel common odds ratio will be weighed towards the larger strata, which carry most of the information.

Miettinen's test-based confidence limits.

Confidence limits are devised to give an impression of the statistical uncertainty involved in the estimation of a given quantity from the available data, such as the estimation of an odds ratio from a case-control study. These limits express that if one went on and on, repeating exactly the same study over and over again, and if one calculated an odds ratio each time, then this odds ratio would show a variability due to chance alone.

To calculate the confidence limits – under the usual Gaussian assumptions – one needs to know the standard error of the estimate, which is nothing but the standard deviation of the set of odds ratios which one would obtain upon performing the study over and over again. Then, taking 1.96 times the standard error at each side of the point estimate, which is the odds ratio from the single study that one has performed, gives the 95 per cent confidence limits. These limits are the boundaries between which the estimate will fluctuate 95 per cent of the times due to chance alone. Only 5 per cent of the times would one have obtained an estimate which would lie outside these limits, that is 2.5 per cent of the times above the upper limit, and 2.5 per cent of the times below the lower limit. From this, one can see how 95 per cent confidence limits also include the concept of statistical significance. When the confidence interval does not include unity – the value of the odds ratio under the null hypothesis of no association – the odds ratio obtained is significantly different from unity at a level of 5 per cent or less.

The reasons that the confidence interval is used instead of the p-value (Rothman 1978) are that:

1) It does not introduce an arbitrary border denoting what "is significant" or what "is not".
2) The reader can judge for himself whether he/she thinks that the statistical variability of the result of a certain study is satisfactory or not. In general, the larger the study, the smaller the confidence interval around the estimate and the smaller the statistical variability.
3) It permits the easy comparison between studies, since confidence intervals calculated for different studies can be plotted to see how much they overlap.

The exact calculation of the standard error of an odds ratio, especially of the odds ratio of a stratified analysis, requires a maximum likelihood estimation. This procedure is not readily transparent to the non-mathematically inclined and, in most cases, cannot easily be calculated on paper or even a desk calculator. Miettinen (1976) introduced an approximation, which has been largely accepted in the epidemiological and statistical literature (Breslow and Day 1980, Kleinbaum and Kupper 1982). To calculate the confidence limits, this approximation makes use of the Mantel-Haenszel Chi – square statistic for stratified data (published in the same 1959 paper as the common odds ratio, but not to be confused with it), whence the name of 'test-based' confidence limits. The formula for calculation is:
$\mathbf{OR_{upper}, OR_{lower}} = \mathbf{exp}[(\mathbf{ln}\ \mathbf{OR})(1 \pm Z_a/X_{MH})]$ where **exp** stands for the natural (Napierian) antilogarithm and **ln** for the natural logarithm, **OR** for the odds ratio found in the study (which can be a Mantel-Haenszel odds ratio), Z_a for the standard normal deviate which corresponds to the desired interval, and X_{MH} for the Mantel-Haenszel Chi (the square root of the Mantel-Haenszel Chi – square statistic). As can be seen from the formula, the confidence limits are calculated on a logarithmic scale, under the assumption that the logarithmic transformation is "normalizing" the sampling distribution of the odds ratio. A discussion of the derivation of this formula can be found in Schlesselman (1982). We will here only indicate the advantages and disadvantages of the test-based procedure. Its advantage, besides the calculation on paper or pocket calculator and the consequent "touch" with the data, is that it makes use of the Mantel-Haenszel Chi-square for stratified data (which can of course also be used when the data are not stratified; then the number of strata is one). Thus, it is consistent with the Mantel-Haenszel statistic: whenever an odds ratio is statistically significant according to the Mantel-Haenszel statistic, the null value unity will fall outside the test-based confidence limits, and vice versa. Its main disadvantage is that it is only exact under the null

hypothesis: the calculated confidence interval tends to become too narrow when the estimated odds ratio is very large or very small (Halperin 1977, Gart and Thomas 1982).

Hardware and software

To obtain tables of exposure frequencies for cases and control patients, stratified for different confounders, the author used the Statistical Package for the Social Sciences (SPSS), as adapted for the PDP-11/40 computer at the Institute of Epidemiology. To calculate the Mantel-Haenszel odds ratio and the test-based confidence limits from these tables, the author used the Hewlett-Packard 97 desk calculator with the programs written by Rothman and Boice (1979).

V.4.2.2 Stratified results

To assess the influence of the individual confounding factors (year of birth, year of first GP visit, menopausal status, marital status and outpatient clinic) we will first present the stratified results for each confounder separately. In the tables, we will give the stratum-specific odds ratios and the Mantel-Haenszel common odds ratio with its 95 per cent confidence limits. At the bottom of each table we will repeat the crude odds ratio and its 95 per cent confidence limits, which were calculated from Table V.5 and already presented in Table V.6. The inspection of the stratum-specific odds ratios permits to verify whether there are individual odds ratios that vary widely from the Mantel-Haenszel common odds ratio. The comparison between the Mantel-Haenszel odds ratio and the crude odds ratio will show whether the stratification for the confounding factor makes much of a difference.

Next, we will evaluate several combinations of these factors. To obtain adequate numbers in each of the categories upon crosstabulation and to reduce the size of the resulting tables, we will then use broader strata, e.g. broader age categories.

Tables V.9 to V.13 give the stratified data for each confounding factor separately. From these analyses, stratified for a single confounder, it appears that the most important confounders are year of birth, year of first GP visit and menopausal status. Table V.14 shows a crosstabulation for year of birth *and* year of first GP visit, using broader strata for each. Table V.15 shows the crosstabulation for year of first GP visit *and* menopausal status. Finally, Table V.16 shows the crosstabulation for year of birth *and* year of first GP visit, but *limited* to those women who were *premenopausal*

TABLE V.9

Odds ratio estimation for different categories of oral-contraceptive use, according to marital status

		Ever	Ex	Current	Never
Married	cases	63	22	41	135
	controls	151	75	79	121
	OR	0.37	0.26	0.46	1
Unmarried	cases	8	3	5	22
	controls	14	8	6	13
	OR	0.34	0.22	0.49	1
Mantel-Haenszel OR		0.37	0.26	0.47	1
95% conf. limits		0.26-0.53	0.16-0.42	0.31-0.72	–
Crude OR		0.36	0.26	0.46	1
95% conf. limits		0.25-0.52	0.16-0.42	0.30-0.70	–

TABLE V.10

Odds ratio estimation for different categories of oral-contraceptive use, according to outpatient clinic

		Ever	Ex	Current	Never
University Leiden	cases	21	6	15	30
	controls	56	32	24	39
	OR	0.49	0.24	0.81	1
University Utrecht	cases	33	12	11	48
	controls	38	19	19	12
	OR	0.22	0.16	0.14	1
Stadsmaten Enschede	cases	7	4	3	13
	controls	19	9	10	30
	OR	0.85	1.03	0.69	1
Municipal Arnhem	cases	14	2	12	39
	controls	32	14	18	26
	OR	0.29	0.10	0.44	1
Ziekenzorg Enschede	cases	6	1	5	27
	controls	23	9	14	27
	OR	0.26	0.11	0.36	1
Mantel-Haenszel OR		0.35	0.22	0.43	1
95% conf. limits		0.25-0.51	0.13-0.37	0.28-0.68	–
Crude OR		0.36	0.26	0.46	1
95% conf. limits		0.25-0.52	0.16-0.42	0.30-0.70	–

TABLE V.11

Odds ratio estimation for different categories of oral-contraceptive use, according to menopausal status (calculated back to time of first GP visit)

		Ever	Ex	Current	Never
Pre-menopausal	cases	65	19	46	148
	controls	137	54	83	111
	OR	0.35	0.26	0.41	1
Post-menopausal	cases	6	6	0	9
	controls	31	29	2	24
	OR	0.52	0.55	0.00	1
Mantel-Haenszel OR		0.37	0.30	0.40	1
95% conf. limits		0.26-0.52	0.18-0.50	0.26-0.62	–
Crude OR		0.36	0.26	0.46	1
95% conf. limits		0.25-0.52	0.16-0.42	0.30-0.70	–

TABLE V.12

Odds ratio estimation for different categories of oral-contraceptive use, according to year of birth

		Ever	Ex	Current	Never
1926-29	cases	12	4	8	44
	controls	33	23	10	54
	OR	0.45	0.22	0.98	1
1930-34	cases	11	6	5	37
	controls	44	26	18	34
	OR	0.23	0.21	0.26	1
1935-39	cases	16	9	7	28
	controls	31	18	13	22
	OR	0.40	0.39	0.42	1
1940-44	cases	11	1	10	29
	controls	29	8	21	10
	OR	0.13	0.04	0.16	1
1945-49	cases	13	4	9	10
	controls	19	6	13	9
	OR	0.62	0.60	0.62	1
1950-56	cases	8	1	7	9
	controls	12	2	10	5
	OR	0.37	0.28	0.39	1
Mantel-Haenszel OR		0.32	0.25	0.40	1
95% conf. limits		0.22-0.47	0.15-0.41	0.26-0.62	–
Crude OR		0.36	0.26	0.46	1
95% conf. limits		0.25-0.52	0.16-0.42	0.30-0.70	–

TABLE V.13

Odds ratio estimation for different categories of oral-contraceptive use, according to (calculated) year of first GP visit for rheumatism

		Ever	Ex	Current	Never
1960-64	cases	2	0	2	28
	controls	0	0	0	10
	OR	+inf	–	+inf	1
1965-69	cases	5	1	4	45
	controls	6	1	5	21
	OR	0.39	0.47	0.37	1
1970-74	cases	22	5	17	38
	controls	25	6	19	27
	OR	0.62	0.59	0.63	1
1975-81	cases	42	19	23	46
	controls	137	76	61	76
	OR	0.51	0.41	0.62	1
Mantel-Haenszel OR		0.54	0.44	0.63	1
95% conf. limits		0.36-0.80	0.26-0.77	0.40-1.0	–
Crude OR		0.36	0.26	0.46	1
95% conf. limits		0.25-0.52	0.16-0.42	0.30-0.70	–

TABLE V.14

Odds ratio estimation for different categories of oral-contraceptive use, relative to never-use, according to year of birth and year of first GP visit

Year of first GP visit	Year of birth		Ever	Ex	Current	Never
1960-74	1926-39	cases	17	6	11	77
		controls	21	5	16	45
		OR	0.47	0.70	0.40	1
	1940-56	cases	12	0	12	34
		controls	10	2	8	13
		OR	0.45	0.00	0.57	1
1975-81	1926-39	cases	24	13	9	32
		controls	87	62	25	65
		OR	0.56	0.42	0.73	1
	1940-56	cases	20	6	14	14
		controls	50	14	36	11
		OR	0.31	0.34	0.30	1
Mantel-Haenszel OR			0.47	0.42	0.48	1
95% conf. limits			0.32-0.70	0.24-0.72	0.30-0.77	–
Crude OR			0.36	0.26	0.46	1
95% conf. limits			0.25-0.52	0.16-0.42	0.30-0.70	–

TABLE V.15

Odds ratio estimation for different categories of oral-contraceptive use, relative to never-use, according to year of first GP visit and menopausal status

Year of first GP visit	Menopausal status		Ever	Ex	Current	Never
1960-74	pre	cases	28	5	23	108
		controls	28	5	23	56
		OR	0.52	0.52	0.52	1
	post	cases	1	1	0	3
		controls	3	2	1	2
		OR	0.22	0.33	0.00	1
1975-81	pre	cases	37	14	23	40
		controls	109	49	60	54
		OR	0.45	0.38	0.52	1
	post	cases	5	5	0	6
		controls	28	27	1	22
		OR	0.65	0.68	0.00	1
Mantel-Haenszel OR			0.49	0.45	0.50	1
95% conf. limits			0.33-0.72	0.26-0.78	0.32-0.79	–
Crude OR			0.36	0.26	0.46	1
95% conf. limits			0.25-0.52	0.16-0.42	0.30-0.70	–

TABLE V.16

Odds ratio estimation for different categories of oral-contraceptive use, relative to never-use, according to year of birth and year of first GP visit, restricted to women who were pre-menopausal

Year of first GP visit	Year of birth		Ever	Ex	Current	Never
1960-74	1926-39	cases	17	5	11	74
		controls	18	3	15	43
		OR	0.55	0.97	0.43	1
	1940-56	cases	12	0	12	34
		controls	10	2	8	13
		OR	0.46	0.00	0.57	1
1975-81	1926-39	cases	17	8	9	26
		controls	62	38	24	43
		OR	0.45	0.34	0.62	1
	1940-56	cases	20	6	14	14
		controls	47	11	36	11
		OR	0.33	0.43	0.30	1
Mantel-Haenszel OR			0.45	0.41	0.47	1
95% conf. limits			0.30-0.69	0.22-0.76	0.29-0.75	–
Crude OR			0.36	0.26	0.46	1
95% conf. limits			0.25-0.52	0.16-0.42	0.30-0.70	–

at that time. Stratification for women who were postmenopausal was not attempted because of the small size of this group. It is apparent that stratification based on combinations of factors increases the odds ratios more than stratification for a single factor. However, all odds ratios remain below or around one-half and are statistically significant at the 5 per cent level.

Moreover, inspection of the odds ratios for each of the strata shows that all remain within a reasonable range of the Mantel-Haenszel common odds ratios. In judging how far off the odds ratio of a single stratum is form the common odds ratio, it should be kept in mind that the stratum-specific odds ratios are based on small numbers, and , in consequence, have wide confidence intervals. The same underlying value seems to apply for the age strata, the different years of first GP visits, all clinics, pre- and postmenopause, and for married and unmarried women. This constancy is taken as evidence against important interactions with any of these confounders.

V.4.3 *Adjustment for confounding by logistic modelling*

The reason for using the logistic model in the analysis of epidemiologic data has never been stated more succintly than by Truett and the late J. Cornfield when they introduced it (1967): *"The traditional analytic method of the epidemiologist, multiple crossclassification, quickly becomes inpracticable as the number of variables to be investigated increases. Thus, if 10 variables are under consideration and each variable is to be studied at only three levels, e.g. serum cholesterol of less than 225 mg/100ml, 225 – 274, and 275 and over, there would be 59,049 cells in the crossclassification. Even with only 10 cases for the denominator of the rate for each cell, a cohort of approximately 600,000 persons would be required."*

What Cornfield wrote within the context of a follow-up study, applies equally well for case-control investigations (Schlesselman 1982). As mentioned in the previous section, a combination of confounders has most influence upon the Mantel-Haenszel odds ratio. However, for practical reasons, we then had to use broader strata, or even discard some of the material where we expected crosstabulation to result essentially in rows of zeros. Nevertheless, one would like to see what the effect would be when several confounders are taken into account at one time. The solution, offered by Cornfield, is the use of the logistic regression. The price that one pays is that the logistic model enforces a particular relation between the odds ratio and the explanatory variables in the logistic model. The benefit

is that the model provides "bridges" over areas with little information in the data. The generally known linear regression has a similar performance and a similar drawback. The assumption behind it is linearity of the relation: thus, one needs in principle only two data points in order to draw the straight line. At the same time, this assumption is a potential weakness, especially when the information present is really scarce, so that only a straight line is possible, the rest of the data consisting of empty cells.

V.4.3.1 Methods: the logistic model

A generally used form of the logistic model is:
$p = [1 + \exp[-(a+bx)]]^{-1}$
where **p** is a probability (range 0 to 1), **exp** is the (Napierian) antilogarithm function, and the interpretation of $(a+bx)$ is similar to that in linear regression: **a** is an intercept, and **b** , the coefficient of the explanatory variable **x** , is a slope. The similarity to linear regression can be seen readily upon rewriting the above formula algebraically as:
$\ln(p/1-p) = a + bx$. Logistic regression analysis can be regarded as the regression of the logarithm of the odds that something will happen, i.e. the odds of becoming diseased. When the variable **x** denotes an exposure which eventually explains the occurrence of the disease and when this is coded as an indicator variable (dummy variable or zero/one variable), the coefficient **b** can be simply interpreted as the logarithm (log) of the odds ratio.

The derivation is easy for the simplest case of one disease and one exposure, denoted by the explanatory variable **x** . Assume the disease is lung cancer and the exposure is yes-or-no smoking. Then, for a smoker the probability of acquiring lung cancer is written as p_1 , and the odds that a smoker will acquire lung cancer are $p_1/1-p_1$. Likewise, for a non-smoker the probability of acquiring lung cancer is p_0 and the odds are $p_0/1-p_0$. The explanatory variable **x** is coded **1** for a smoker and **0** for a non-smoker. One can then write two logistic regressions:
for smokers: $\ln(p_1/1-p_1) = a + b$ (where **x** is **1**), and
for non-smokers: $\ln(p_0/1-p_0) = a$ (where **x** is **0**).
The ratio of these two odds is obtained by subtracting the logarithms of the odds:
$\ln(p_1/1-p_1) - \ln(p_0/1-p_0) = (a + b) - a = b$,
or $\ln[(p_1/1-p_1)/(p_0/1-p_0)] = b$.
Thus, the logarithm of the odds ratio equals **b** . The antilogarithm of this coefficient, e^b , gives the odds ratio for the risk of getting the disease, which in a case-control study is estimated by the exposure odds ratio. A mathematically more detailed account can be found, in order of increasing statistical sophistication, in Schlesselman (1982), Kleinbaum, Kupper and Morgenstern (1982) and Breslow and Day (1980).

When more than one variable is entered into the model,
e.g. $\ln(p/1-p) = a + b_1x_1 + b_2x_2$, the interpretation is also analogous to that for linear regression. Expressed intuitively, b_1 is the increase in the log odds due to a "change" in exposure status, i.e. the log odds ratio when exposure is compared with non-exposure, under the condition that the other variable in the model, x_2, does not change its value. This is exactly what we wanted to accomplish by crosstabulation: comparing like with like, i.e. keeping all other variation constant. Regression analysis is often referred to as the "poor man's experiment".

The above reasoning already indicates how we used the logistic model. We regarded it as a somewhat more sophisticated form of cross-stratification. We would watch the coefficient of the exposure variable, the log of the odds ratio of interest, to see how it changes upon the introduction of other variables that are potential confounders. In principle, we are interested in neither the magnitude of the other coefficients or their significance, nor the overall explanatory power of the model.

In our use of the logistic model, we entered all variables as indicator variables. The exposures we were interested in were ever-use, ex-use and current-use, relative to never-use of the pill. To estimate the crude effect of ever-use, we wrote the simplest model with only one explanatory variable which was coded "1" for ever-users and "0" for never-users. When we wanted to estimate the crude effect of ex- and current-use, we wrote a model with two indicator variables, one for ex-use and one for current-use. The indicator for ex-use became "1" for ex-users and "0" otherwise; the indicator for current-use became "1" for current-users and "0" otherwise. Therefore, the reference category when *both* indicator variables were entered simultaneously was the category of the never-users. We must always enter both indicators together in this model: if we should enter only one, say the current-use indicator, then the reference category would become a mixture of ex- and never-users.

To adjust for the effects of confounders, we entered the potential confounders one by one as indicator variables. Confounders that were numerically continuous, such as year of birth, were entered as a set of indicator variables. This is accomplished by splitting a continuous variable, such as year of birth, into a number of strata, say six, and then replacing it by a set of five indicator variables, one for each stratum except the reference stratum. The process is illustrated in Table V.17.

The category 1926-29 becomes the reference category for year of birth. Now, the coefficient b_1 of x_1 will represent the "effect" of the age category 1930-34 relative to the category 1926-29 to explain "caseness" in

TABLE V.17

Indicator	1926-29	1930-34	1935-39	1940-44	1945-49	1950-56
x_1	0	1	0	0	0	0
x_2	0	0	1	0	0	0
x_3	0	0	0	1	0	0
x_4	0	0	0	0	1	0
x_5	0	0	0	0	0	1

this case-control study, the coefficient b_2 will represent the contrast between 1935-39 and 1926-29, etc.

The transformation of a continuous variable to a set of indicator variables has the following advantages:

1) It removes part of the model constraints. As mentioned in the introduction to this section on the logistic model, the logistic regression imposes linearity of the log odds, something which is not only difficult to conceive of, but might not even represent anything near the true state of nature. For example, if one should enter "year of birth" as a continuous variable, e.g. by entering age in its natural units in the model, then the model would try to fit a line through the age values which is linear in the log odds: this would give age an exponential effect on the risk of being a case of rheumatoid arthritis in this case-control study. In contrast, by the use of age categories with indicator variables, each age category "floats" independently of the others, relative to the reference category. Together, this set of variables can model any given age effect, be it exponential or otherwise. An accurate modelling of the confounder is important in trying to remove its effect from the effects of the exposure in which we are really interested.

2) The maximum likelihood computation on the computer is more efficient.

The iterative process takes less computer time and is more reliable as far as rounding off errors are concerned.

A drawback of the use of sets of indicator variables is that not many confounders can be entered at one time. There is a limit on the number of such dichotomising variables that data can support, without dichotomising the information away. Fortunately, in our analysis the iteration never failed because of the introduction of too many dichotomies.

Hardware and software.

The computer algorithm for the maximum likelihood estimation of the coefficients of the logistic model and their 95 per cent confidence limits is based on Lee (1974). This algorithm was adapted and an additional rule for stopping the iteration was introduced by P.I.M. Schmitz, Department of Biostatistics, Erasmus University. The adapted program was translated into BASIC for the PDP 11/40 computer by A. van Laar, and incorporated into the data analytic package that was developed at the Institute of Epidemiology by dr. L.K.J. van Romunde. This package permits to read the raw data, aggregate similar records, perform Elementary Data Analysis (Tukey 1980), switch back and forth to SPSS and BMDP system files, and enter data into the logistic program.

V.4.3.2 Results of the logistic analysis

Table V.18 shows the odds ratios for the different categories of pill use, as calculated from the coefficients of the logistic model, upon successive inclusion of several confounders. The detailed logistic regression is given in Appendices F and G.

Upon the successive inclusion of more confounders in the model the odds ratios increase, but remain below or around one-half and stay statistically significant. Moreover, the final odds ratios are close to the ones obtained with the Mantel-Haenszel computation after multiple crosstabulation (see Section V.4.2.2). As in the univariate analysis, the greatest effect was found for controlling for year of birth and year of first GP visit; control for menopausal status had a less pronounced effect in the logistic regression. Surprisingly, outpatient clinic, which we had entered last in the model, since it had had no effect in the univariate analysis, did have an effect in the multivariate analysis – conditional upon the presence of the other confounders in the model. As in the univariate analysis, there was no gradient between ex- and current-users of the pill: this contrasts with the findings of the Royal College of General Practitioner's Oral

TABLE V.18

Odds ratio estimated for different categories of oral-contraceptive use, relative to never-use, by the logistic model[1], upon cumulative[2] inclusion of potential confounders in the model[3]

Confounder	Ever	Ex	Current	Never
None	0.36 (0.25-0.52)[4]	0.26 (0.15-0.42)	0.46 (0.30-0.71)	1 –
Year of birth	0.32 (0.22-0.46)	0.25 (0.15-0.42)	0.38 (0.24-0.60)	1 –
Year of first GP visit	0.48 (0.32-0.72)	0.43 (0.25-0.75)	0.51 (0.31-0.82)	1 –
Marital status	0.48 (0.32-0.73)	0.43 (0.25-0.76)	0.52 (0.32-0.84)	1 –
Menopausal status	0.49 (0.32-0.74)	0.47 (0.27-0.82)	0.50 (0.31-0.81)	1 –
Outpatient clinic	0.42 (0.27-0.65)	0.40 (0.22-0.72)	0.46 (0.27-0.75)	1 –

[1] Estimated as $OR = e^b$, where b is logistic regression coefficient.

[2] Variables entered in same sequence: None, year of birth, year of birth and year of first GP visit, etc., untill all confounders in the model.

[3] Details of regression analysis in Appendices G and H.

[4] 95 per cent confidence interval.

Contraception Study in which the negative association was confined to current-users (see Chapter II.1, and discussion in Chapter VI)

V.4.4 *Duration of oral-contraceptive use*

An important consideration in judging epidemiologic inference is always whether there is a dose-response relationship in the data. Often this is interpreted as strengthening assumptions of causality, despite the commentary by Weiss (1981). A search for a dose-response relationship in data on the pill and rheumatoid arthritis can be approached from two directions: either look at the oestrogenic or progestogenic content of the pill or at the duration of use. We have no information concerning the type of oral contraceptives used, so we must limit this analysis to the duration-response relation.

Duration of pill use was approximated by calculating the time lapsed between the first use of the pill and the last use before the first GP visit for rheumatism. If the pill was still being taken at the time of the first GP visit, the date of the visit was taken as the last time the pill was used. Of course, some women stopped taking the pill for a while in between these two dates. This induces some misclassification, especially for those in the category of "prolonged" pill use, since occasionally the pill was discontinued for longer periods in between the first and the last date of use.

We first looked at the distribution of the duration of pill use by two-year categories; see Table V.19.

Next, we tried to identify a duration-response relationship by means of the logistic model. For this purpose, the duration of use was transformed in a set of indicator variables which form a cascade. A first indicator for ever-use, a second for use lasting two years or more and a third for use lasting four years or more. The cascade coding is given in Table V.20.

From the table it can be seen that whenever the pill is used at all, x_1 becomes **1** . As soon as use exceeds two years, x_2 also becomes **1** . Thus, the coefficient of x_1 , which is b_1 , gives the effect of less than two years of use relative to never-use. Likewise the coefficient of x_2 , b_2 , gives the effect of more than two years of use, but less than four, relative to that of less than two years of use. Again, this cascade system is introduced to avoid imposing some specific form upon the duration-effect relationship.

We entered these indicator variables together with all confounders in the logistic model. Table V.21 presents the coefficients of the indicator variables, their standard error, the odds ratios and their 95 per cent confidence limits.

TABLE V.19

Duration of pill use preceding first GP visit

Duration[1]	numbers (per cent)
Never-use	304 (54.6)
< 2 yrs	60 (10.8)
2-< 4 yrs	40 (7.2)
4-< 6 yrs	38 (6.8)
6-< 8 yrs	47 (8.4)
8-< 10 yrs	68 (12.2)

[1] One woman's duration of use is missing.

TABLE V.20

	x_1	x_2	x_3
Never-use	0	0	0
<2 yrs	1	0	0
2 -<4 yrs	1	1	0
4+ yrs	1	1	1

TABLE V.21

Logistic regression coefficients and odds ratios calculated by e^b for different categories of OC use, adjusted[1] for all confounders

Effect of	Relative to	Coeff.(s.e)	OR	95 per cent conf. int. of OR
<2yrs	Never-use	−0.735(0.339)	0.48	0.25-0.93
2-<4yrs	<2yrs	−0.221(0.479)	0.80	0.31-2.05
4+ yrs	2-<4yrs	0.117(0.427)	1.12	0.49-2.60

[1] Logistic model with: year of birth, year of first GP visit, marital status, menopausal status and clinic; other coefficients not shown here.

From this table, one can also calculate the overall effect of any category relative to never-use by multiplying: e.g. the effect of two to four years of use relative to never-use is 0.48x0.80, or 0.38, and the effect of more than four years of use relative to never-use becomes 0.48x0.80x1.12, or 0.43.

From these results it appears that the major impact of the pill is already apparent after less than two year of use. To explore this further, we performed an analysis using one-year categories for the duration of pill use. The one-year categories are shown in Table V.22.

TABLE V.22
Duration of pill use preceding first GP visit, finer stratification

Duration[1]	numbers (per cent)
Never-use	304 (54.6)
< 1 yr	34 (6.1)
1-< 2 yrs	26 (4.7)
2+ yrs	193 (34.6)

[1] Duration of use of one woman is missing.

Indicator variables were computed using the same cascade technique, and entered in the logistic regression model; see Table V.23. Here, the major effect is already apparent after one year of use. There is no additional effect of a second year and a slight additional effect after more than two years of use. We concluded that these data do not present a clear duration-response relationship. The implications are discussed in Chapter VI.2.

V.4.5 *Subgroup analysis of cases and control patients*

In Table V.4A and V.4B, it became apparent that there existed some differences within the case-group between seropositive and seronegative patients, and within the control-group between the soft tissue rheumatism,

TABLE V.23

Logistic regression coefficients and odds ratios calculated by e^b for different categories of OC use, adjusted[1] for all confounders

Effect of	Relative to	Coeff.(s.e)	OR	95 per cent conf. int. of OR
<1yr	Never-use	−0.737(0.417)	0.48	0.21-1.08
1-<2yrs	<1yr	−0.000(0.619)	1.00	0.29-3.36
2+ yrs	1-<2yrs	−0.131(0.510)	0.88	0.32-2.38

[1] Adjusted for year of birth, year of first GP visit, marital status, menopausal status and clinic.

osteoarthritis and the miscellaneous categories. The question naturally arises whether the negative association of rheumatoid arthritis with pill use will also hold for each of the subgroups.

The distribution of the frequencies of pill use according to subgroup is presented in Table V.24.

Ever-use is more frequent among the seronegative patients. It is, however, possible that adjustment for confounders would affect these comparisons. Therefore, to test the consistency of the findings, we performed the four different case-control analyses that are possible with this material. Using the odds ratio calculated for ever-use, we compared 1) seropositive RA with soft tissue rheumatism, 2)seropositive RA with osteoarthritis, 3) seronegative RA with soft tissue rheumatism, and 4) seronegative RA with osteoarthritis. Thus, we omitted the "others" category from these comparisons. The results are shown in Table V.25. The negative association proved somewhat stronger in the seropositive group.

V.4.6 *Analysis with different exposure definition*

In Section V.2 we mentioned that the case and control patients gave somewhat different reasons for taking the pill. The cases who had used the

TABLE V.24

Frequencies of oral-contraceptive use, in subgroups of cases and control patients[1]

		Ever	Ex	Current	Never
Cases	Seropos RA	39(27.4)	12(8.1)	27(18.1)	109(73.6)
	Seroneg RA	32(40.1)	13(16.3)	19(23.8)	48(59.9)
	All	71(31.1)	25(11.0)	46(20.1)	157(68.9)
Controls	Soft Tissue	96(57.1)	44(26.2)	52(31.0)	72(42.9)
	Osteoarthr.	50(46.7)	31(29.0)	19(17.8)	57(53.3)
	Others	22(81.5)	8(29.6)	14(51.9)	5(18.5)
	All	168(55.6)	83(27.5)	85(28.1)	134(44.4)

[1] Percentages in brackets.

TABLE V.25

Odds ratio (and 95% confidence interval) estimates for ever-use in different contrasts between subgroups of cases and controls

Group	Odds ratio[1]
Seropositive RA vs soft tissue rheumatism	0.37(0.21-0.66)
Seropositive RA vs osteoarthritis	0.38(0.20-0.76)
Seronegative RA vs soft tissue rheumatism	0.61(0.31-1.19)
Seronegative RA vs osteoarthritis	0.56(0.24-1.30)

[1] Adjusted for year of birth, year of first GP visit, marital status, menopausal status and outpatient clinic.

pill before the onset of rheumatism, did so more often for contraceptive purposes than the controls. As this could be due to a hidden bias in the control group – which might consist of women who were more medicalised – we also performed an analysis in which exposure was restricted to pill use for contraceptive purposes only. Pill use for non-contraceptive purposes was coded as never-use in this analysis. The results for the different categories of exposure are given in Table V.26. As expected, this redefinition weakened the association slightly, in comparison with the original results in Table V.18. All odds ratios remained around one-half, however, and were statistically significant at the 5 per cent level.

TABLE V.26

Odds ratios for different categories of pill use, relative to never-use, calculated by the logistic model. Exposure defined as pill use for contraceptive purposes only.

	Ever	Ex	Current	Never
OR[1]	0.56	0.51	0.60	1
95% conf. limits	0.36-0.87	0.28-0.93	0.36-1.00	–

[1] Adjusted for year of birth, year of first GP visit, marital status, menopausal status and clinic.

V.4.7 *Summary of the analysis*

The analysis was started by discarding several of the questionnaires because of incompleteness or because of lack of informativeness. We have already indicated why we do not think that this biased the final results.

The precise definition of exposure to oral contraceptives presented some difficulties, which were solved basically by recalling that our aim was to investigate pill use in relation to the onset of disease. We decided to use

the calculated date of the first GP visit for rheumatism as an approximation of this onset.

The differences in characteristics between cases and control patients, such as age, year of first GP visit, marital status, menopausal status and clinic, indicated that the crude results should not be taken at face value. Adjustment for possible confounders was performed firstly by crosstabulation and secondly by logistic modelling. Both showed increases in the odds ratios up to about one-half. When three variables were included in the crosstabulation, the adjusted odds ratios were close to those computed with the logistic model using all potential confounders. There was no gradient between ex- and current-use of the pill, in contrast to the findings of the Royal College of General Practitioner's Oral Contraception Study.

There was a weak gradient of the odds ratio with duration of pill use. Pill use of more than two years duration had a slightly more negative association than pill use of less than one year.

The subgroup analyses of cases and control patients showed that the negative association held when case and control groups were split into the major subgroups, and that the negative association was somewhat stronger for seropositive patients.

Redefinition of exposure as being pill use for contraceptive purposes only resulted in slight increases of the odds ratios, but all remained around one-half and stayed statistically significant at the 5 per cent level.

CHAPTER VI
DISCUSSION

VI.1 Weighing the present investigation

The odds ratio calculated from this case-control study was almost the same as the rate-ratio determined in the General Practitioner's Oral Contraception Study. While this numerical similarity might immediately lead to acceptance of the idea that the pill indeed halves the incidence of rheumatoid arthritis, we believe that greater caution is indicated. The present case-control study was a non-experimental investigation, as was the Royal College's study. Although pure hazard seems an unlikely explanation for the similarity between the odds ratio and the rate-ratio, the same bias could be present in both studies. In the review of the literature in Chapter II.1 we expressed our hesitations in accepting the earlier results; in fact, we had not expected to confirm the negative association. Because of these considerations, we want to evaluate our results carefully on the basis of their own merits. This evaluation will proceed along the lines that are generally accepted for weighing the evidence of this type of non-experimental research: in turn we will treat selection bias, information bias, disease and exposure misclassification and confounding bias.

VI.1.1 Selection bias

The first point to be considered in the evaluation of a case-control study is the selection of cases and controls. Both groups of patients were sampled from existing files. Thus, all represent prevalent states of the disease at the time of our inquiry. In principle, prevalent cases can yield valid odds ratio estimates, on the condition that the survival of cases and controls is not affected differentially by the exposure of interest (Miettinen 1976). It is unlikely that this condition would not be met in this investigation. Furthermore, either a positive or a negative selection with respect to the exposure seems unlikely. One cannot imagine that the diagnosis of rheumatoid arthritis and/or the referral pattern would be influenced by the physicians knowledge of the patient's oral-contraceptive use.

For the control patients, the discussion about possible selection bias amounts to the discussion about the choice of a control group. We chose a clinical series of control patients from two major diagnostic categories of rheumatic disease, which cover a wide variety of illnesses that differ in kind, duration and severity. This variety was considered a safeguard against unknown associations between these control diagnoses and oral-contraceptive use (Jick and Vessey 1978). In addition, during the planning of this study we were in the fortunate position of being able to compare in another setting the frequency of oral-contraceptive use among women with soft tissue rheumatism and/or osteoarthritis with that for the general population. For this purpose we could use the data from the EPOZ-study, as described in Chapter III.2.3. During this cross-sectional population survey of 10,532 persons, conducted earlier by the Institute of Epidemiology, data had been collected on both the use of oral contraceptives and the prevalence of clinical rheumatic conditions. Information about these two items had been collected in different parts of the survey as the present hypothesis was not yet known. These population survey data permitted us to compare the frequency of pill use for women suffering from the more common types of soft tissue rheumatism and/or osteoarthritis, with that in women who did not suffer from any of these conditions. No differences emerged. Moreover, the overall order of magnitude of ever-use of oral contraceptives in the different age categories compares well between the present study (see Table V.12) and the EPOZ data (see Tables III.2 to III.7). We would not expect complete comparability, since the contraceptive experience in our case-control study covers globally an earlier calendar period.

During the process of the verification of the diagnoses, we removed the patients with major concurrent diseases (cardiovascular, cancer, psychiatric). This was performed for potential cases and controls in exactly the same way (Feinstein and Horwitz 1982). It so happened that more potential controls were excluded by this criterion, presumably because of selective referral of patients who were treated in other medical departments of the same hospital. This happened most frequently in the clinics of the teaching hospitals.

In the analysis of the present case-control study, we have shown that splitting the control group up into its two major components (soft tissue rheumatism and osteoarthritis) did not affect the odds ratio estimates. Nevertheless, we were still worried that the reasons for oral-contraceptive use were somewhat different between cases and controls: cases indicated "to prevent pregnancy" more often as reason for pill use than controls. This could suggest that cases and controls differed in type: maybe some of the women who consult a physician on soft tissue rheumatism or miscellaneous arthralgias are more medicalised or have more complaints in general, which could lead to a more frequent use of oral contraceptives for heavy or irregular menses. However, we found significant odds ratios of the same order of magnitude after redefining exposure as being pill use for contraceptive purposes only.

VI.1.2 *Information bias*

A second major point in the evaluation of a case-control study is recall, response and observer bias. The fact that all of our control patients also had rheumatic complaints made it very natural to inquire into the dates of onset of rheumatism and the dates of oral-contraceptive use in a questionnaire accompanied by a covering letter which was the same for cases and controls. Cases and controls were therefore unaware of the hypothesis involved. A further guarantee against differential bias between cases and controls is the uniformly high response rate. As a guarantee against observer bias, all codings of the exposure were checked upon by a computer algorithm (see Table IV.2).

VI.1.3 *Misclassification*

VI.1.3.1 Disease Misclassification

As described in the earlier chapters, the analysis of this case-control study was restricted to "probable" and "definite" cases of rheumatoid arthritis, defined according to the guidelines of the American Rheumatism Association (Ropes et al. 1957). This probability labelling of the diagnosis is indicated by the rheumatologist on the forms which are used to register the patients in the diagnostic rheumatology registry in Rotterdam. Together with the diagnosis, the degree of its certainty was verified in this investigation by checking whether it was maintained on subsequent visits. It is, however, always possible that some diagnostic misclassification occurred; this is particularly likely in the "probable" category which contributed 10 per cent of the cases (Harris 1981). Conversely, some of the controls may happen to develop the full clinical picture of rheumatoid arthritis in the future. The effect of this type of diagnostic misclassification is to dilute the strenght of the association. This can be seen intuitively. If in truth there are less pill takers among women with rheumatoid arthritis (the cases) than among a control group of women without the disease, then the inclusion of some misdiagnosed women without the disease in the case group will increase the number of pill takers in that group. The contrast between the case and the control groups will therefore diminish, and the odds ratio will tend to become unity. By a similar reasoning, the presence of women with rheumatoid arthritis in the control group will have the same effect upon the odds ratio. In conclusion, we are not unduly worried by the possibility of some diagnostic misclassification in this case-control study, since it can only mean that the true odds ratio is even smaller than the odds ratio of one-half which we found.

VI.1.3.2 Exposure Misclassification

While the use of prevalent cases of the disease will not invalidate the odds ratio estimation, it is a drawback as far as the accuracy of the information is concerned: cases and controls had to recall dates of pill use out of a more or less distant past. Inevitably, this will induce some misclassification of the exposure in cases and controls alike.

That misclassification between the categories of pill use did occur in this study, became apparent during the analysis. First, during the coding of the questionnaires, an arbitrary choice had to be made when a woman had

indicated two possible months or even two possible calendar years for the date of first specialist consultation or for the dates of pill use. Second, the date of first GP visit for rheumatism, which was the dividing line for the exposure categories, was calculated from the data, i.e. from the date of the first specialist consultation and the delay between GP and specialist consultation as indicated by the woman. Obviously, the latter will only indicate the correct order of magnitude, but not give the exact number of days. Third, the calculation of the duration of exposure was approximate, since it made only use of the first and the last dates of pill use, and did not take into account intermittent pill use.

Exposure misclassification in case-control studies also tends to dilute associations that are real (Breslow and Day 1980). Thus, if this type of misclassification was present in our data, the true odds ratio gradients between the categories of oral-contraceptive use are stronger than the ones we found. Misclassification is least likely to have occurred in the distinction between ever- and never-use. In this study, most of the never-users, defined as non-use before the first GP visit, were absolute never-users, i.e. they had never taken the pill up to the date our questionnaire. In contrast, some degree of misclassification might explain the absence of a clear relationship with the duration of pill use as well as the difference between our findings and the findings of the Royal College of General Practitioner's study concerning past use of the pill.

VI.1.4 *Confounding bias*

A last point in the evaluation of a case-control study is the control of confounding. Differences emerged between case and control patients, which could, in and by themselves, lead to higher or lower frequencies of oral-contraceptive use in one of the groups: year of birth, year of first GP visit (due to secular trends in oral-contraceptive use (Shapiro et al. 1981)), menopausal status and marital status. Control for those potential confounders together with control for outpatient clinic somewhat increased the odds ratio estimates, although for all exposure categories they stayed around or below one-half, and remained statistically significant. It should be noted that the odds ratio estimate was influenced most by the adjustments for year of birth, time of the first GP visit and menopausal status. The influence of adjustment for clinic in the univariate analysis was different from that in the multivariate analysis. However, both types of analysis essentially yielded the same adjusted odds ratios.

Since this study is non-experimental, one can always wonder whether

there were any hidden or unknown confounders which caused the negative association and could explain our findings. It has been suggested that the number of pregnancies (parity) might be a confounder. Pregnancy might correlate with pill use later in life or in between pregnancies. In addition, pregnancy has an ameliorating effect on rheumatoid arthritis. If it also has a preventive effect, which is only speculative at present, then pregnancy might act as a confounder. We had not asked questions about the number of pregnancies or children to keep our questionnaire short.

Of course, one can always speculate about other confounders. If one does, one should always be able to explain their positive association with the disease and their negative association with pill use, or vice versa. At present we cannot visualize any factor that fulfils these criteria.

VI.2 The pill and rheumatoid arthritis: general conclusions and indications for further research

The discussion of the previous paragraphs leads to the conclusion that our investigation was valid internally, i.e. we accept the conclusion of a negative association between the pill and rheumatoid arthritis in this study population in the Netherlands. How then do these results affect our attitude towards the more global hypothesis that the pill prevents rheumatoid arthritis?

Our findings are consistent with those of the earlier follow-up study and the secular trend study discussed in Chapter II.1. There are important differences however. In the follow-up study by the Royal College of General Practitioners, the benefit was confined to the current-users. Ex-users showed none. In our investigation, the benefit seems to be equally large for current-users and for ex-users. It is hardly likely that the latter finding reflects a true state of nature. It is difficult to conceive how pill use in the past could provide the same protective effect indefinitely. Most likely, our discrimination between ex- and current-users is less exact than that of the Royal College of General Practitioner's study. In our study the classification of the exposure depended upon a calculation which in turn was based on the memory of the participants. In contrast, in the General Practitioner's study the classification depended upon notification by the GP at the enrollment of the subject and during later follow-up visits in the course of the study. A prospective follow-up offers often a better chance to classify exposure status more correctly. A main difference with respect to the findings from the Mayo Clinic's registry is that the potential causative agent responsible for the decrease in the incidence of rheumatoid arthritis

in Rochester, Minnesota, could only be hypothesised vaguely as some form of female hormone that was marketed since the early 1960s.

Two more cautionary remarks about possible generalizations based on this study and other studies are in order. As yet, the findings only apply to caucasian females who took the pill in the early seventies, since most of the information, in both the Royal College's study and ours, concerns pill use in that period by women of caucasian stock. As the pharmacological content of the pill has changed since that time, it remains an open question whether this negative association and possible preventive effect still exist today. Similarly it is not known whether the findings apply to other races.

However, despite all cautions, the finding of a negative association remains. It has now been established in a follow-up study and a case-control study, and was indicated in a secular trend study. It fits a general recurring interest in the relation between female hormones and rheumatoid arthritis. Yet, the negative association will be more easily acceptable to the immunologically minded rheumatologist when a plausible mechanism for this action is proposed. Indeed, despite the similar outcome and the individual strengths of the different epidemiologic studies, the possibility of some unknown confounding factor remains, since all of these investigations were non-experimental. It is inconceivable that a randomized controlled trial will ever be set up to test the hypothesis experimentally. As a result, acceptance of causality will necessitate the demonstration of the underlying biological mechanism.

In his first major paper on the beneficial effects of pregnancy upon the course of rheumatoid arthritis, Hench (1938) quotes a woman sighing that she ought to keep pregnant all the time. In the early days of the pill, its effect was described to the lay public, and to the profession as well, as the induction of a state of pseudo-pregnancy. It is tempting to link the wish of Hench's patient to this general description of the mode of action of the pill in an effort to explain its effects on the onset of rheumatoid arthritis.

Hench himself refused much speculation, but specifically mentioned that the association with pregnancy does not in itself mean that the mechanism involves female hormones. When it became known that plasma corticosteroid levels rise up to threefold during pregnancy (Dixon et al. 1967), it seemed logical to ascribe the pregnancy effect to this phenomenon, particularly since rheumatologists are familiar with the dramatic effects of corticosteroids on the symptoms of rheumatoid arthritis. However, this rise in plasma corticosteroids is mainly, and perhaps entirely, accounted for by a corresponding rise in the corticoid-binding globulin concentration (Dixon et al. 1967). Therefore, it is still unclear which biologic effects these

changes in corticosteroid metabolism could have. A recent editorial about the influences of pregnancy upon immunologic diseases stresses our present ignorance about the basic mechanism (Denman 1982). In the best tradition of Hench, it is stated that the possible mechanisms need not necessarily be hormonal. An ingenious hypothesis, involving a graft of fetal suppressor cells to a suppressor-deficient mother is discussed (Froelich et al. 1980). The search for the "pregnancy factor" is still a subject of active immunologic research, and some success is being reported. A review of the abstracts of the VIIIth Pan-American Congress of Rheumatology, held in June 1982, reveals that two papers were devoted to the identification of a pregnancy associated alpha-glycoprotein with immunosuppressive effects (Persellin et al. 1982, Unger et al. 1982), and a third described the in vitro immunosuppressive effect of pregnancy serum components (Russell et al. 1982). In addition, a decreased level of helper T-cells was recently discussed as a possible cause of immunodeficiency in pregnancy (Sridana et al. 1982).

We can imagine that investigators will feel the need to repeat the present case-control experience with incident cases only, with in depth personal interviewing by trained personel, focussing on current brands of oral contraceptives and using other control groups, to ensure that this piece of the hormone-rheumatoid arthritis puzzle is a real one. A more general program for clinical and epidemiologic investigations to advance our insight and eventually to guide basic research, could include several of the following questions:

– does the pill also have a preventive effect against juvenile rheumatoid arthritis?

– is there a difference in preventive effect depending upon the pharmacological content of the pill, i.e. oestrogens vs. progestogens?

– does postmenopausal oestrogen substitution also have a preventive effect against rheumatoid arthritis?

– does an early (natural or artificial) menopause influence the incidence of rheumatoid arthritis?

– do pregnancies affect the incidence of rheumatoid arthritis, and does this effect differ in pre- and postmenopausal women?

– in addition to the possible preventive effects of synthetic female hormones, are there also curative effects (clinical amelioration) comparable to the effect of pregnancy? Is this curative effect the same in women who experience an amelioration during pregnancy in comparison with women who do not experience such an amelioration?

It is of interest to note that some of the questions relating to the menopause and pregnancy have already been addressed partially in the

older literature. They are discussed in detail in the report of a case-control study on rheumatoid arthritis by Short, Bauer and Reynolds (1957). No relationship with the age or the nature of menopause was found. Pregnancy was only studied in relation with the time of onset of the disease. An apparent increase in incidence after delivery was explained as the effect of a masking of the early manifestations of the disease during pregnancy.

Further studies might take place under the more general heading of "hormones and immunologic disease", with a special interest in female hormones since women are at greater risk for these diseases (Inman 1978). The two diseases studied most often in this respect are systemic lupus erythematosus and rheumatoid arthritis. It is not easy to see a consistent pattern in the clinical information. As discussed, pregnancy has a beneficial upon the clinical course of rheumatoid arthritis (Hench 1938, Persellin et al. 1979). However, this effect is limited to the period of pregnancy, and might be followed by an aggravation in the postpartum period (at the time of the reappearance of menses). The pill would have a protective effect against the development of rheumatoid arthritis. Its influence upon the clinical course has only received scant attention (Gill 1968, Bole et al. 1969). The influence of pregnancy upon the course of systemic lupus is still being debated. Some hold that it aggravates the disease, while others confirm that it does not (Denman 1982). Oral contraceptives are believed more or less universally to aggravate systemic lupus, even to induce a relapse. However, a recent report drew a distinction between combined contraceptive preparations and the progestogen-only preparations (Jungers et al. 1982). The latter would not influence the course of systemic lupus negatively. The same authors also find a marked detrimental effect of pregnancy. One wonders how to reconcile these findings.

In basic immunologic research, some pieces already fit together, while others do not. First, there are the experiments on hormonal influences in mice which spontaneously develop lupus erythematosus (Inman 1978, Talal et al. 1980): androgens retard the development of the disease, while oestrogens enhance it. This has been proven by both pharmacological and castration experiments. Second, there are the reports on oestrogens receptors in articular cartilage, more specifically in chondrocytes (Peter et al. 1982, Rosner et al. 1982a). Third, there are the in vitro experiments on the effect of oestradiol on B-cell maturation, mediated via an inhibition of suppressor T-cells (Paavonen et al. 1981). Fourth, there are the beneficial effects of anti-oestrogen therapy on experimental osteoarthritis in rabbits (Rosner et al. 1982b). Fifth, there is the earlier report on an immuno-suppressive effect of oral contraceptives, which was said to be similar to,

although not as strong as that of pregnancy (Barnes et al. 1974). Finally, the theories on a direct effect of female hormones on cellular immunity still have to rival with the earlier insights on the effect of oral contraceptives on plasma corticosteroid and corticoid-binding globulin concentration, which are also similar to those described in pregnancy (Riad-Fahmy et al. 1979).

If any generalisation is possible from these diverse clinical, experimental and laboratory findings, it would be that pregnancy has an effect on T-cell function, possibly either mediated by a serum glycoprotein or by corticosteroid metabolism, thereby bringing temporary relief of the suffering of rheumatoid arthritis. Some components of the pill have a similar, although less outspoken, effect on cellular immunity. It still is difficult to reconcile these ideas with the findings concerning lupus erythematosus. Maybe systemic lupus and rheumatoid arthritis should be viewed separately to clarify the picture. In addition, the components of the pill do not have the same chemical structure as the naturally occurring hormones. Differences in chemical structure might have important immunological consequences. As so often in the sciences, progress might rather come from making distinctions instead of lumping together several diseases or several agents. To explain the protective effect of the pill, we hypothesize that, as a result of either its own hormonal content or by the alteration of endogeneous biological activity of hormones, this agent might create an hormonal milieu which does not allow the ultimate "trigger" of rheumatoid arthritis to exert its effect. This "trigger" could be an antigenic stimulus like, for example, changes in the intestinal bacterial flora (Bennet 1981).

VI.3 Possible influence upon the image of the pill: public health implications

Over the past few years there has been growing concern about the cardiovascular side effects of the pill. In the United States, some estimates of the – mainly cardiovascular – deaths due to the pill have been made (Stadel 1981) : *"Among women who do not smoke cigarettes the annual risk of death associated with current use of oral contraceptives increases from about 1 per 100,000 among women 15 to 19 years old to about 3 per 100,000 among those 30 to 34 and to around 18 among those 40 to 44. In women under 35 years of age, these figures are one fourth or less of the risk associated with complications of pregnancy among women using no method of contraception, and they are similar to the risk of death associated with current use of other methods of contraception"*. Cigarette smoking increases the extra risk of oral

contraceptives about three-fold. It now appears that the pill has the potential to halve the incidence of rheumatoid arthritis, a disease with an incidence of about 1 per 1000 and a prevalence of about 2 per cent for adult females (Hochberg 1981, Linos et al. 1980, Allander and Bjelle 1981). This would mean that cumulatively 1 pill taker out of 100 might be spared many years of suffering, disablement and handicap.

One wonders whether some formal cost-benefit analysis would not show that such savings (decades of drug consumption and medical care) offset the economic loss arising from the rare cardiovascular event caused by the pill?

In a similarly controversial area, the prescription of oestrogen replacement therapy in the post-menopause, formal cost-benefit analysis has yielded interesting results (Weinstein 1980). Oestrogen replacement therapy in the postmenopause increases the likelihood of uterine cancer. On the other hand, it reduces postmenopausal osteoporosis and thus the incidence of life threatening and disabling fractures of the hip or forearm in elderly women. From the dollar point of view, it appears that the few induced cancer deaths might be balanced by the economic savings on hospitalisations for fractures.

In view of the concern about the cardiovascular side-effects of oral contraceptives, the following general guidelines have been proposed – originally by the presidents of the Royal College of General Practitioners and the Royal College of Gynaecologists (Kuennsberg and Dewhurst 1977). As long as a woman is younger than about 30 years old, a non-smoker and not hypertensive, the pill is the safest method of contraception, from the point of view of both effective contraception and possible side effects. In the presence of a combination of cardiovascular risk factors, the risk of the pill for a woman below 30 years of age is not really higher than that of other methods of contraception and/or pregnancy. This situation rapidly reverses for a woman over 30 years of age. The balance of risks and benefits becomes unfavourable for the pill with increasing age, particularly so if other cardiovascular risk factors are present. On the basis of these guidelines, a woman can decide for herself – together with her GP. One wonders whether the negative association between the pill and rheumatoid arthritis, if interpreted causally, will change this view much. From a cost-benefit point of view, it is likely to increase the age at which the risks of the pill outweigh its benefits or the risks of other modes of contraception. This would be due to the fact that the cardiovascular side effects, both the induced suffering and the monetary cost, will be partially cancelled out by the benefits for potential rheumatoid arthritis patients. What will be the

practical consequence of such actuarial manipulations? We view the latter as being rather artificial, since the cardiovascular risk of the pill is perceived mainly as premature cardiovascular death, while the benefit is the possible postponement of years of disablement. For the individual who has to decide, these are two rather incomparable quantities. One can imagine that different individuals will decide differently about such small risks with such important consequences.

Of course, no woman will take contraceptives in order to prevent rheumatoid arthritis. Nevertheless, women stop taking the pill due to fear of its side-effects (Shapiro et al. 1981, Population Reports 1982). In the Netherlands, concern about the side-effects of the pill seems to have resulted in an increased demand for abortion (Ketting 1981). The pill has been an important factor in liberating women from unwanted pregnancies. Therefore, it might be a good thing to present first of all a balanced view of the risks involved. In addition, the message that the pill prevents a rheumatic disease which is frequent in women could add a note of optimism to the discussion. If this allays unnecessary fears in women on-the-pill, we consider this to be a positive result of our undertaking.

CHAPTER VII
LOOKING BACK WITH JOY

In this final chapter, we want to look back and reflect critically on what we could have done differently, or what others could do better in the future. We will deal with case selection, questionnaire construction, practical sample size considerations and reactions of patients and physicians to the undertaking.

VII.1 Patient selection

VII.1.1 *The use of the registry*

One reason that prompted us to embark on this study was the availability of a registry of rheumatologic outpatients as well as inpatients of several of the larger rheumatology clinics in the Netherlands. For one participating center, however, the use of the information compiled in the registry was not feasible due to a change in the patient identification system. For that one center, we had to use the outpatient records, i.e. the outpatient appointment schedules. In the end this worked out fine, although it did mean that one secretary had to carry out an extensive search for files, diagnoses etc. Now the question arises: did we really need the registry? Could the same study not have been based on local registrations of patients,

such as appointment schedules or diagnostic registers which already exist? In principle, the answer is yes, of course. In practice, we doubt it. Several practical reasons lead us to hope that the central registry will remain in existence, and flourish. Firstly, true diagnostic registration of the outpatients of a rheumatology clinic is rare, as discussed in Chapter II.4. Local registration – if uniform – could be valuable. For several of the participants, however, the registry maintained at the Institute of Epidemiology is the only *diagnostic* registry available. The participating rheumatologists use it to gain insight into their own patient material or to mount their own research projects. Secondly, outpatient records such as appointment schedules, are not of uniform quality and usefulness. In principle they can be used as an approximation of a diagnostic registry if diagnosis and year of birth, or age, are listed. When one of these is lacking, their usefulness as a "sampling frame" for epidemiologic purposes is none, since it would be necessary to look up all medical records one by one. Thirdly, the bonds existing between the institute and the practising physicians made them rather accessible to the idea of using the registry for this kind of study.

Thus, although uniform local patient and diagnosis registration, or even well-kept outpatient records, could replace the central registry for our purposes, we believe that uniformity and accessability would be difficult to maintain. It would be even more difficult than with a central registry, due to lack of interest and knowledge about data processing by busy rheumatologists. If we had had to rely upon existing local registrations and/or patient records, this would have added at least an additional year of slow and tedious preparation of lists of names of potential cases and controls.

One drawback of the registry in its present form should be noted. For the purpose of safeguarding the patient's right to privacy and medical confidentiality, the present registry is anonymous. The individual patient is only identifiable by a number that is identical to the identification number in the files at the rheumatologist's office. This means that to obtain lists of names and addresses, the rheumatologist's secretary received an extra work-load. This extra work could be circumvented easily. On the registration form that is sent to the Institute of Epidemiology, there is a place for the patient's name and address. In most hospitals this is already filled in, for administrative ease, but often erased out before sending the form off to Rotterdam. If not obliterated, the forms have to be destroyed anyway. When, in the future, a copy of the name and address could be stored somewhere on computer tape together with the identification

number, the search for patients for any kind of study would be greatly facilitated. Of course, one would need technical guarantees for preserving privacy and confidentiality. This could be achieved by storing the connection between names and identification numbers in a different place than the connection between diagnoses and identification numbers, and permitting access to the former only after formal permission of the attending rheumatologist.

VII.1.2 *Selection of incident and prevalent patients*

In this study we chose to use both incident patients (new patients visiting the outpatient clinic) and prevalent patients (patients coming for a follow-up visit). The reasons for this approach were:

(1) larger numbers would be available immediately – after all, rheumatoid arthritis is a disease with a very low incidence among young women,

(2) it was difficult to differentiate between the two in the registry,

(3) in principle, it is hard to define an incident case of rheumatism: most patients will already have been treated by their GPs and often also by other specialists before coming to a particular outpatient clinic.

In the analysis stage, we were confronted with the drawbacks of this choice.

Three findings emerged:

(1) about 15 per cent of patients had complaints which dated from before the 1960s, so that they were non-informative as far as the hypothesis questioned in this investigation is concerned,

(2) the case group tended to include more chronic patients than the control group: the year of first contact with the medical system was on the average earlier for the cases than for the controls. In addition, the delay within the medical system (between GP and specialist) was different between cases and controls,

(3) part of the problem with misclassification between the exposure categories, as discussed in Chapter VI.1.3, was due to the fact that patients were asked to recall events occurring around the onset of their disease, which for prevalent cases of rheumatism could be 10, 15 or even 20 years ago.

The first two problems proved surmountable, the first by excluding about 15 per cent of the material, and the second by statistical adjustment, i.e. stratification for calendar year of first GP visit in the analysis. The third problem, misclassification, was apparently not strong enough as to wipe out

the negative association altogether, but was probably the cause of the weakness of the dose-response relationship and the absence of an odds ratio gradient between ex- and current-users, neither of which are easy to explain under causal assumptions.

In principle, incident cases of rheumatism which are collected prospectively (at the time of the investigation) will not present any of these problems. However, the investigation would proceed much more slowly, unless the number of participating rheumatologists was larger. Furthermore, prospective patient enrollment would have required continuous efforts on the part of the participating rheumatologists (in signaling patients eligible for the study), whereas now only a one-time effort for identification and diagnostic verification was necessary. We judged that neither the money, nor the enthousiasm would have been present to embark on such an ambitious undertaking concerning an hypothesis which was still only the chance finding of one study.

We were fortunate that we initially had set out for large enough numbers of cases and controls. This enabled us to exclude 15 per cent, and yet to retain enough information for crosstabulation according to the year of first GP visit. If a conclusion emerges, it is that any collection of data will contain some inaccuracies and unusable material, so that more data should be collected than estimated on the ground of statistical sample size alone, even after correction for response rates.

VII.1.3 *Unusable patient records*

A rather large number of patient records was not usable; sometimes because of lacking or incomplete diagnostic information, but generally because of concurrent diseases. The original lists drawn from the computer files and the outpatient records contained many more patients than the 465 cases and 386 controls who were eligible to be enrolled and to receive letters. A numerical feel for this problem can be obtained from Table IV.1 by looking at the difference between "selected from registry" and "questionnaires mailed". Roughly, this loss of material can be estimated to be another 10 to 15 per cent, which should be taken into account when determining the sample size.

VII.2 The questionnaire

VII.2.1 *Poorly understood questions*

Despite the pilot study and our careful review of the questionnaire, one question caused difficulties and another was so poorly completed that it had to be discarded.

The question that many women found difficult was "Do you still have your periods regularly". Several women wrote down extra information on the questionnaire, such as: "I still have them, but not regularly". On the basis of such information, the author, who coded the information, was usually able to classify the women as either premenopausal or postmenopausal, which sufficed for the analysis purposes.

The question that was so poorly completed that it was discarded, was the one concerning the reasons for not using oral contraceptives. It read "If you have never taken 'the pill', was this because you.....". The answers included: "used no contraceptives", "wished to become pregnant", but also "used other methods to prevent pregnancies". This provoked the written comment from one participant that she was amazed to find such a poorly worded question in a professional questionnaire. The author meant to say: "preferred a different way to avoid becoming pregnant (temperature method a.o.)". The patients had apparently thought that this phrase referred to "other devices", as some of them indicated. Several of the married women acknowledged "non-use", while indicating only a limited number of pregnancies.

The question about the reasons for not taking the pill was posed as a final check of the comparability of cases and controls, if ever a difference in pill use between cases and controls would emerge. Fortunately, the complementary question about the reasons for taking the pill was presented more clearly: "If YES, why did you use the pill". Since a difference in the reasons for pill use was indeed found between cases and controls, we used the information from the latter question to correct for this difference in the analysis (Chapter V.4.6).

In conclusion, a questionnaire cannot be checked too carefully, and yet, despite many precautions, misunderstandings will occur.

VII.2.2 *Unusable questionnaires*

About 10 per cent of the questionnaires could not be processed due to poor completion – despite the assurances of several female

collaborators that this questionnaire would not cause any woman any problem.

Maybe, we should have stated more clearly in the instructions accompanying the questionnaire that even approximate dates should be filled in, under the assumption that the error rate would be the same for cases and controls. Another possibility would have been to pretest the questionnaire more extensively, maybe by having it filled in by patients in our presence. Whatever the solution, one plays safe by augmenting the desired sample size by another 10 per cent.

VII.2.3 *Exposure definition*

As explained in detail in Chapter VI.1.3, in several respects the nature of our data collection resulted in exposure misclassification, with a consequent dilution of the observed odds ratio. Most important was that the date of the first rheumatologic symptoms was approximated by the date of the first GP consultation for these symptoms, and that the latter was in turn approximated by subtracting two pieces of information volunteered by the patient: the date of the first specialist consultation for rheumatism and the delay between the GP and the specialist consultation.

This source of inaccuracy could have been partially removed by asking for the date of the first symptoms or the date of the first GP consultation directly. We did not do so, as explained in Chapter III.2.6, because we feared that the patients would have difficulties in remembering these dates. However, a succession of questions about dates and the intervals between them might have been feasible, even on a written questionnaire. It would provide the patient with an internal check when filling out the form, and could thus enhance accuracy. It is difficult to know whether personal interviewing would have yielded more reliable answers. Patients might well have felt pressed to answer at once without taking the time for the necessary reflection.

If this case-control study is ever repeated to study the dose-response relationship better, an attempt should be made to obtain a more accurate definition of the exposure by trying to get more accurate dates.

VII.2.4 *Questions not asked*

Three kinds of questions which were not asked in the present questionnaire might nevertheless merit consideration for future studies:

(1) The number of pregnancies (parity).

This could in principle be a hidden confounder. See Chapter VI.1.4. As already mentioned, we are of the opinion that the association between pregnancy and rheumatoid arthritis is a subject for future exploration.

(2) The "brand" of pill.

This was not included in our questionnaire, because we were afraid that asking too much detail might deter participation. After all, the original hypothesis did not specify a particular type of oral contraceptive. Nevertheless, further exploration of the hypothesis might necessitate an investigation of this issue.

(3) Other oestrogens.

We did not inquire into the use of substitution oestrogens since the women were selected on the basis of age, so that most were expected to be premenopausal – at least at the onset of rheumatism. Postmenopausal substitution would again be an important topic in a study of older women who develop arthritis.

VII.3 Sample size considerations in practice

In the preceding paragraphs, we mentioned several times that data had to be discarded, or that records were not usable for a variety of reasons. In chronological order the main reasons for cumulative loss of material were (figures rounded off):

(1) a 10 to 15 per cent loss due to concurrent disease or other problems regarding the diagnosis,

(2) a 15 per cent loss due to non-response,

(3) a 10 per cent loss due to poor completion,

(4) a 15 per cent loss due to onset of rheumatism before 1960, i.e. exposure impossible,

(5) a 10 per cent loss of cases of rheumatoid arthritis due to uncertainty of the diagnosis (the "possibles").

Furthermore, there were small losses due to non-identificability, un-tracability and double indexing.

Since all losses are cumulative, a total of about 40 to 50 per cent of the theoretically available material was not used. Not all of these types of loss will occur to the same extent in all case-control investigations which make use of mailed questionnaires and sample patients from a registry. Nevertheless, it might be a safe rule to increase the sample sizes to handle these losses. A rule of thumb could be that the sample size should be almost twice the sample size needed for statistical power considerations. At the same time, it should be remembered that all sample size calculations for

statistical purposes concern only the "overall" results. In most investigations, it is likely that subgroups will be analysed, and even be included in the final report. Generally, it cannot be foreseen what these subgroup analyses will be like. It is wise to add extra cases and controls in anticipation of these analyses: say, another 10 per cent.

To increase the amount of collected to twice what is needed for statistical purposes will certainly increase the cost of the investigation. This should be remembered when considering the attractions of a relatively low-cost mailed questionnaire case-control study based on a registry.

VII.4 Reactions of patients and physicians to participation in the investigation

Despite the very friendly relations between the participating rheumatologists and the investigators in the Institute of Epidemiology, which harbours the diagnostic registry, we quickly became aware that several issues were sensitive. Firstly, the rheumatologists objected to any direct mailed approach of their patients on the institute's letterhead. Secondly, even though the letter was written on their own stationary and was to be signed by them, some of the rheumatologists voiced the concern that their patients would be upset.

In practice, fewer than five patients explicitely refused to participate. About a dozen dialed the central number in Rotterdam for further information about the investigation. As far as we know, no physician received any complaints from any patient, and only occasionally inquiries into the investigation. In contrast, numerous patients expressed their thanks on the questionnaire and wished us success in our investigation which they hoped would solve some of the problems of the disease which caused them so much suffering. Many added detailed personal notes about their lives, particularly about contraception.

The pattern sketched above is a recurrent one. There is physician anxiety about the consequences of approaching the patient, which sharply contrasts with the patient's general willingness to participate in research of this type. We have witnessed this pattern often in investigations carried out in the Institute of Epidemiology. In his Ph.D. thesis, Vermeer (1981) describes the example of pediatricians who worried about their patient's reactions to an outsider inquiring into the late results of surgery of the lower uro-genital tract; in contrast, many parents and patients were relieved that the surgical results were being checked again. In another recent investigation drs. van Steensel-Moll (personal communication), who

supervises a case-control study in parents of children with leukaemia, has had to face the doubts of many pediatricians as to the wisdom of stirring up unhappy memories in parents whose child has died, sometimes several years ago. In practice, there were no objections from the parents; on the contrary, many expressed their gratitude for the effort. Recently, these problems were considered in a Personal View paper in the British Medical Journal (Bellman 1982), and in an editorial (Rothman 1981) accompanying two papers in the American Journal of Public Health. The Personal View concerned the experiences of an investigator who interviewed the parents of mentally handicapped, and sometimes already deceased, children. His comments can only be quoted in full: *"In order to comply with medical ethics, we needed consent from a child's own doctor before contacting parents. Many participants commented that this should have been the other way round. The doctor often expressed reservations about our visiting the families as, it was suggested, they might resent further interference and probing into their personal tragedies. I found that nothing could be further from the truth. In all my visits with the doctor's consent the reaction of the family was joy that "someone was taking an interest" and investigating the brain illness of which they had a tragic experience. Even, or perhaps especially, the parents of the dead children responded this way. ... The thought that they had contributed to research was obviously a great comfort to the parents."* The editorial in the American Journal of Public Health voices in quite strong terms an Epidemiologist's Laments about the reservations on the part of physicians and ethical committees concerning epidemiologic research projects, especially because patients often prove to be very receptive. Of course, in the U.S. the physician's fears are augmented by the possibility of litigation; nevertheless, the arguments presented by each side sound familiar. In the editorialized papers (Herrman et al. 1981, Funch et al. 1981) it is described how the epidemiologist had to struggle to obtain physician's and hospital's cooperation, and how, when the study was finally running, – after many delays and much interference – he/she was the only one to witness the patient's gratitude and enthousiasm.

Fortunately, our relations with the rheumatologists were excellent due to the long-standing links with investigators in the Institute of Epidemiology. At the end of the investigation, the patients were informed about the study's results in a joint letter of thanks, by agreement of all participating rheumatologists. (See Appendices I and J).

One emerging lesson is that people are motivated by a genuine willingness to collaborate in a research project which may ultimately help to relieve others from the disease that has affected them or their relatives.

Another lesson is that to overcome problems about the acceptability of this type of research, it might be advisable for an epidemiologist to specialize in a certain disease area and to have established contacts with physicians who treat patients for the disease in question.

SAMENVATTING

Hoofdstuk I beschrijft de voorgeschiedenis van dit onderzoek: de berichten in de medische literatuur over de preventieve werking van "de pil" op reumatoide arthritis die onze aandacht trokken, de eerste ideeën over de wijze waarop deze hypothese kon worden getoetst, en de mogelijkheden die hiervoor bestonden op het Instituut Epidemiologie van de Erasmus Universiteit Rotterdam. Het doel van het onderzoek werd omschreven als: nagaan, of de halvering van de incidentie van reumatoide arthritis bij pilgebruiksters in vergelijking met niet-pilgebruiksters, zoals beschreven in een vervolgonderzoek in Groot Brittannië, ook wordt gevonden in een case-control onderzoek in Nederland.

Hoofdstuk II gaat verder in op de redenen om dit onderzoek op te zetten. Eerst wordt de literatuur kritisch beschouwd. De gegevens die wijzen op het bestaan van een negatief verband tussen het gebruik van "de pil" en het optreden van reumatoide arthritis, zijn interessant, doch vergen nadere bevestiging: tegen de validiteit van de gevolgtrekking zijn verschillende bezwaren in te brengen. Vervolgens is er een belang voor de maatschappelijke gezondheidszorg. Als "de pil" inderdaad bescherming zou bieden tegen het ontstaan van een invaliderende ziekte die bij vrouwen veel voorkomt, dan zou dit een zeker tegenwicht kunnen bieden tegen de negatieve publiciteit over de cardiovasculaire neveneffecten van "de pil". Daarnaast is er een belangrijk fundamenteel wetenschappelijk belang. Als "de pil" het ontstaan van reumatoide arthritis causaal tegengaat, dan levert dit wellicht een nieuw stukje in de legpuzzel van de pathogenese van deze ziekte. De laatste reden om aan dit onderzoek te beginnen was de unieke mogelijkheid geboden door een reuma-registratie, die de patienten van verschillende grote reumatologische poliklinieken in Nederland omvat.

Hoofdstuk III geeft details over het theoretische hoe en waarom van dit onderzoek. Waarom het een case-control onderzoek moest zijn. Waarom wij prevalente ziektegevallen gebruikten. Hoe en waarom een postenquete is gebruikt om de benodigde informatie te verzamelen over het gebruik van orale contraceptiva (de "exposure" die ons interesseerde). Dit hoofdstuk eindigt met enige beschouwingen over de kunst van het schrijven van begeleidende brieven.

Hoofdstuk IV geeft de realiteit weer: hoe het onderzoek werkelijk verliep. Eerst waren er de moeilijkheden in verband met de identificatie van de patiënten: de overeenkomst met de patiëntenidentificatie op de poli-

klinieken was minder goed dan wij ons hadden voorgesteld. Daarna wordt de selektie van "cases" en "controls" in de verschillende poliklinieken beschreven. Het hoofdstuk behandelt verder de verzending van de enquete, de respons, de herinneringsbrief en de moeilijkheden bij het coderen van de gegevens.

Hoofdstuk V presenteert de resultaten van het onderzoek, dat wil zeggen de analyse van de enquetegegevens. Bij deze analyse moesten we opnieuw de onderverdeling in de verschillende "exposure"-categorieën kritisch overdenken: de codering kon worden gerelateerd aan het eerste huisartsenbezoek voor reuma, of aan eerste contact met de specialist. Aangezien onze belangstelling uitging naar voorkómen van het ontstaan van reumatoide arthritis, besloten wij, om het gebruik van orale contraceptiva te relateren aan het moment dat het dichtst bij het ontstaan van de ziekte lag. Dit is dan het eerste huisartsencontact voor reuma. Vervolgens werden we geconfronteerd met de problemen van de "verstorende" variabelen. In een aantal opzichten verschilden "cases" en "controls", en deze verschillen konden op zichzelf reeds aanleiding zijn tot het vinden van een hogere of lagere mate van "exposure" in één van beide groepen: leeftijd, ogenblik van eerste contact met de huisarts, huwelijkse staat, optreden van de menopauze en bezochte polikliniek. Eerst zijn telkens een paar van deze verstorende variabelen verwerkt in eenvoudige kruistabellen. Daarna gebruikten wij het logistische model om met alle relevante verstorende variablen tegelijk rekening te houden. De analysefase werd afgerond door subgroepen van "cases" en "controls" nader te analyseren, door het effect van de duur van het pilgebruik na te gaan, en door de analyse over te doen met een iets andere definitie van de "exposure", nl. als pilgebruik uitsluitend voor contraceptieve doeleinden. Hoe wij dit materiaal ook analyseerden, de odds ratio voor het blootgesteld zijn aan pilgebruik schommelde rond een half en bleef statistisch significant op een niveau van vijf percent of minder. Aangezien de odds ratio een benadering oplevert van de rate ratio (de verhouding van de incidentie van de ziekte bij pilgebruiksters t.o.v. die bij niet-gebruiksters), betekent dit dat onze bevindingen de halvering van de incidentie van reumatoide arthritis bij pilgebruik bevestigen.

Hoofdstuk VI bespreekt eerst een aantal aspecten van de opzet van het onderzoek in het licht van onze ervaringen met de gegevensverzameling en de analyse: de selectie van "cases" en "controls", de kwaliteit van de informatie, misclassificatie en verstorende variabelen. Aangezien wij geen belangrijke redenen hebben gevonden waarom de resultaten niet betrouwbaar zouden zijn, hebben wij vervolgens onze aandacht gericht op de consequenties van onze bevindingen. Deze voeren ons terug naar de

beweegredenen voor het onderzoek, die zijn vermeld in Hoofdstuk II. Achtereenvolgens bespreken wij de algemene hypothese van een preventief effect van "de pil" op het ontstaan van reumatoide arthritis, de mogelijke richting die verder epidemiologisch en immunologisch onderzoek zou kunnen volgen en de pro's en contra's van "pil"-gebruik.

Hoofdstuk VII is de epicrise: wat zouden we anders doen als we het onderzoek zouden overdoen? We proberen aan te geven welke problemen we in opzet en analyse hebben overschat, en welke onderschat. Het hoofdstuk eindigt met enige overwegingen betreffende de aanvaardbaarheid van dit type onderzoek voor patient en arts.

SUMMARY

In Chapter I the history of the investigation is described: the literature reports that the pill would halve the incidence of rheumatoid arthritis which first drew our attention, our initial views on how to test this hypothesis by means of a case-control study, and the opportunity presented by the rheumatologic registry at the Erasmus University Rotterdam. The aim of the study is stated: to investigate whether the halving of the incidence of rheumatoid arthritis among oral-contraceptive users relative to never-users, as originally described in a follow-up study in Great Britain, would also be demonstrable in a case-control study in the Netherlands.

In Chapter II the reasons for starting the investigation are elaborated. First, the relevant literature is critically reviewed. The evidence for a negative association between oral-contraceptive use and the development of rheumatoid arthritis is judged interesting, although still wanting: several objections to the validity of the inference can be formulated. Second, the phenomenon is interesting from a point of view of public health. If the pill protects against a crippling disease which is frequent in women, this might to a certain extent balance the negative aspects of its cardiovascular side-effects. Third, there is a strong biological interest. If the pill causally prevents rheumatoid arthritis, this provides another piece of the puzzle of the pathogenesis of this disease, which advances the state of our knowledge. The fourth and last reason for starting the investigation was the unique opportunity of a rheumatology registry that covers the patients of several of the major rheumatology clinics in the Netherlands.

Chapter III examines in detail the theoretical considerations which formed the basis of our investigation. Why it should be a case-control study. Why we used prevalent disease states. Why the controls were to be other patients with rheumatism. Why and how a mailed questionnaire was used to collect the information about the exposure of interest, i.e. oral-contraceptive use. The chapter ends with some reflections on the art of writing covering letters.

Chapter IV presents reality: how the investigation really proceeded. We started with difficulties about patient identification: the link with the outpatient clinic's patient identification was not as straightforward as originally thought. Next the selection of the cases and the controls from the different participating outpatient clinics is described. Also described in this

chapter are the mailing, the response rates, the reminder and the difficulties encountered in coding the information.

In Chapter V the results, i.e. the analysis of the returned questionnaires, are described. During the analysis phase of this study we first had to think once again about the definition of the exposure categories: whether this should be relative to the first General Practitioner contact for rheumatism or relative to the first specialist contact for the disease. Since our interest was with the prevention of the onset of the disease, we decided that we needed information on oral-contraceptive use at a moment in time which would be as close as possible to the onset of the disease. This would be the GP contact for rheumatism. Next we were confronted with the problem of confounding; several factors differed between cases and controls, and could, in and by themselves, explain higher or lower exposure rates in one of the groups: age, time of first GP visit, marital status, menopausal status and clinic. The confounders were first controlled for by simple crosstabulation, involving one to three factors at a time. Then, we used the logistic model to be able to take all relevant confounders into account at one time. The analysis was completed by studying case and control subgroups, duration of pill use and a slightly different exposure definition, i.e. pill use for contraceptive purposes only. By and large, whatever the analysis, the exposure odds ratio stayed around one-half and remained statistically significant at the five per cent level. Since the exposure odds ratio is an estimation of the incidence rate-ratio, this result means that we confirm that the incidence of rheumatoid arthritis among women who use the pill is one-half that among women who have never used oral-contraceptives.

In Chapter VI the different design features of the investigation are discussed in the light of our experience with the data collection and with the analysis: selection of cases and choice of controls, quality of the information, misclassification and confounding. Since no major reason for invalidating the results was found, we then concentrated on the consequences of our findings. This means going back to the reasons for starting the investigation as described in Chapter II. In turn, the general hypothesis of a preventive effect of the pill against rheumatoid arthritis, the possible direction of further epidemiological and immunological research, and the risks and benefits of oral-contraceptive use are considered.

Chapter VII is a reflection: what should we do differently if we were to start again. We tried to assess the design and analysis problems which were underestimated or overestimated. The chapter ends with some

thoughts on the acceptability of this type of research for the patients and their physicians.

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APPENDICES

APPENDIX A
DUTCH COVERING LETTER

J. W. BOERSMA, A. P. HARTMAN en J. WEBER
REUMATOLOGEN
spreekuur volgens afspraak
fondsl. tel. 433241
partic. tel. 423297

ARNHEM, Dec. 1981
Gemeente Ziekenhuis

Geachte Mevrouw,

De laatste jaren is steeds duidelijker geworden, dat gewrichtsklachten kunnen worden beïnvloed door hormonen. In samenwerking met Prof. dr. H.A. Valkenburg van de Erasmus Universiteit in Rotterdam, willen wij daarom nagaan of één veelgebruikt hormoonpreparaat, "de pil" (oraal anticonceptiemiddel), van invloed is op gewrichtsklachten. Bovendien willen wij onderzoeken of die eventuele invloed gunstig is of niet.
Dit is de reden dat wij aan een groot aantal patienten die op de Reumatologische Polikliniek van het Gemeente Ziekenhuis zijn behandeld, de hierbij ingesloten vragenlijst toesturen, met het verzoek om deze in te vullen en in de bijgesloten antwoord-enveloppe terug te sturen. Ook aan u richten wij dit verzoek. Op andere plaatsen in Nederland gebeurt hetzelfde.

Gewrichtspijnen komen zeer veel voor en veel Nederlandse vrouwen gebruiken "de pil". Als er een verband zou bestaan tussen gewrichtsklachten en "de pil", is dit van groot belang voor de gezondheid van de Nederlandse vrouw en van andere vrouwen in de wereld.
Voor dit onderzoek zouden wij u niet alléén vragen willen stellen over het "pil"-gebruik, maar ook over de menstruatie en mogelijke operaties aan de baarmoeder. Alle gegevens over uw ziekte, en alle antwoorden die u geeft, vallen onder het medische beroepsgeheim. Wij staan volledig voor geheimhouding in.

Wilt u de toelichting bij de vragen goed doorlezen vóórdat u de vragen beantwoordt? Aan het einde van de vragenlijst is er ruimte voor uw opmerkingen en vragen. De lijst kunt u in de bruine antwoord-enveloppe zonder postzegel terugsturen aan Prof. dr. H.A. Valkenburg. Zodra de resultaten van het onderzoek bekend zijn, zullen wij u op de hoogte stellen.
Mocht u onmiddellijk inlichtingen wensen over deze vragenlijsten, dan kunt u die telefonisch vragen, 's morgens tussen 10 en 12 op nummer 010-634463 van de Erasmus Universiteit.

Wij hopen van harte dat u aan dit onderzoek wilt medewerken, waarvoor wij u bij voorbaat zeer hartelijk willen danken.

J. W. Boersma, reumatoloog
A.P. Hartman, reumatoloog
dr. J. Weber reumatoloog

APPENDIX B
TRANSLATION OF COVERING LETTER

Dear Madam,

In the past few years, it has become apparent that joint complaints may be influenced by hormones. In cooperation with Prof. dr. H.A. Valkenburg of the Erasmus University of Rotterdam, we want to investigate whether one commonly used hormonal preparation, "the pill" (oral contraceptive), influences joint complaints. If so, we want to find out whether this influence is beneficial or not. This is the reason that we have mailed the enclosed questionnaire to a large number of women who have been treated at the Rheumatology Outpatient Clinic of the Arnhem Municipal Hospital, with the request to complete the form and mail it back. You are one of these women. In other places in the Netherlands, similar investigations are being carried out.

Joint aches and pains are very common and many Dutch women use "the pill". If there is any link between joint complaints and "the pill", this would be very important for the health of Dutch women as well as other women in the world.

This questionnaire contains not only questions about "the pill" but also about your menstrual periods and eventual gynecological operations. All matters concerning your disease and all of your answers will remain confidential. We guarantee that all information will be treated as medical secret.

Please, read the instructions with the questions carefully before filling out the form. At the end of the questionnaire, there is room for *your* remarks and questions. The questionnaire can be returned in the brown return envelope addressed to Prof. dr. H.A. Valkenburg. As soon as this investigation is completed, we will let you know what the results turned out to be.

If you have any immediate questions concerning this questionnaire, please phone us at the Erasmus University (tel. number 010-634463) between 10 and 12 AM.

We hope that you will want to cooperate in this investigation, and we would like to take this opportunity to thank you for doing so.

Sincerely,

APPENDIX C
DUTCH RHEUMATISM QUESTIONNAIRE

V R A G E N L I J S T R E U M A

UW ANTWOORDEN OP DEZE VRAGENLIJST ZIJN MEDISCH GEHEIM.
WILT U DE VRAGENLIJST VOLLEDIG EN DUIDELIJK INVULLEN,
LIEFST MET BALLPOINT.

HET NUMMER VAN DEZE VRAGENLIJST IS:

De eerste vragen gaan over gewrichtsklachten waarvan u mogelijk lang geleden last had, maar waarvoor u uiteindelijk naar een specialist (reumatoloog, internist, orthopedist, neuroloog of andere) bent gegaan.

---

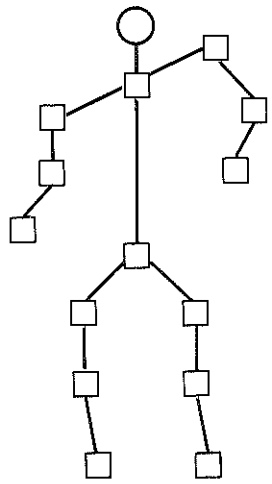
1. Weet u nog, bij benadering, hoeveel weken, maanden of jaren, u al bij uw huisarts in behandeling was voor uw gewrichtsklachten voordat u de eerste keer naar de specialist bent gegaan?
   Vul één cijfer in, bijvoorbeeld: 3 maanden als uw huisarts u na drie maanden had doorverwezen.

..... weken

..... maanden

..... jaren

2. Kunt u op dit poppetje aankruisen waar de pijn zat toen u de eerste keer naar de specialist bent gegaan?
   Zet een kruisje in één of meer hokjes waar u pijn had.



3. In welke maand van welk jaar bent u voor de eerste keer naar de specialist gegaan, wegens deze gewrichtsklachten?
Als u de maand niet meer zeker weet, dan mag u er twee invullen, bijvoorbeeld: maart of april van het jaar 1963.

..... maand ..... jaar

Nu volgen enige vragen over de ongesteldheden (menstruatie).

---

4. Bent u nog geregeld ongesteld? Zet een kruisje in het juiste hokje.

JA ☐ NEEN ☐

(Als u op deze vraag JA antwoordt, mag u meteen doorgaan naar vraag nr. 7)

5. Zo NEEN, hoe oud was u toen u de laatste maal ongesteld was?

..... jaren oud

6. Wilt u aanduiden hoe de ongesteldheden weggebleven zijn? Het juiste aankruisen.

- De baarmoeder of eierstokken zijn operatief verwijderd, en daarna zijn de ongesteldheden weggebleven: JA ☐ NEEN ☐
- De ongesteldheden zijn uit zichzelf weggebleven: JA ☐ NEEN ☐
- Andere: (gaarne voluit omschrijven) .....

.....

De laatste vragen gaan over het gebruik van "de pil".

---

7. Heeft u ooit "de pil" gebruikt? Het juiste aankruisen.

JA ☐ NEEN ☐

(Als u op deze vraag NEEN antwoordt, mag u meteen doorgaan naar nr. 10)

8. Zo JA, waarom gebruikte u "de pil"? Het juiste aankruisen. Meerdere antwoorden zijn mogelijk.

- Om niet zwanger te worden: JA ☐ NEEN ☐
- Wegens pijnlijke ongesteldheden: JA ☐ NEEN ☐
- Wegens onregelmatige ongesteldheden: JA ☐ NEEN ☐
- Andere: (gaarne voluit omschrijven) .....

.....

9. Kunt u, zo nauwkeurig mogelijk, de perioden in uw leven aangeven waarin u "de pil" ononderbroken gebruikte?
Noem maand en jaartal, bijvoorbeeld: VAN maart 1973 TOT september 1975.

	VAN		TOT	
	Maand	Jaar	Maand	Jaar
1.	.....	.....	.....	.....
2.	.....	.....	.....	.....
3.	.....	.....	.....	.....
4.	.....	.....	.....	.....
5.	.....	.....	.....	.....
6.	.....	.....	.....	.....

10. Zo u NOOIT in uw leven "de pil" hebt gebruikt, was dat dan omdat u:
(meerdere antwoorden mogelijk)

- Geen voorbehoedsmiddelen gebruikte: JA ☐ NEEN ☐
- Andere middelen gebruikte ter voorkoming van zwangerschap: JA ☐ NEEN ☐
- Wenste zwanger te worden: JA ☐ NEEN ☐
- Andere: (gaarne voluit omschrijven) .....

.....

---

11. Deze ruimte is bestemd voor uw opmerkingen en vragen bij deze vragenlijst.

Wilt u de volledig ingevulde vragenlijst in de bijgevoegde bruine antwoordenveloppe waarop u GEEN postzegel hoeft te plakken, versturen aan Prof. dr. H.A. Valkenburg, Instituut Epidemiologie, Erasmus Universiteit Rotterdam.

DANK VOOR UW MEDEWERKING.

APPENDIX D
TRANSLATION OF RHEUMATISM QUESTIONNAIRE

YOUR ANSWERS TO THIS QUESTIONNAIRE ARE CONFIDENTIAL. PLEASE, FILL IN THE QUESTIONNAIRE COMPLETELY AND CLEARLY, PREFERABLY WITH A BALLPOINT PEN.

THE NUMBER OF THIS QUESTIONNAIRE IS:

The first questions concern joint complaints which may have developed a long time ago but which ultimately caused you to see a specialist (rheumatologist, internist, surgeon, neurologist or others).

---

1. Do you know, approximately, how many weeks, months or years you were been treated by your General Practitioner before you consulted a specialist for the first time?

Give one number; for example: 3 months, if your General Practitioner referred you to the specialist after three months.

..... weeks
..... months
..... years

2. Could you indicate on this figure where the pain was when you first went to the specialist?

Check one or more boxes where you had pain.

See Dutch questionnaire for drawing.

3. In which month of which year did you go to a specialist for the first time because of these joint complaints?

If you are no longer sure of the month, you may fill in two, for example: March or April of the year 1963.

..... month ..... year

The following questions concern your menstrual periods.

---

4. Do you still have your periods regularily? Check the right answer.

....YES ....NO

5. If NO, how old were you at the time of your last periods?

..... years old

6. Could you indicate how the periods stopped? Check the right answer.

– the womb or ovaries were removed surgically, and the periods subsequently ceased ....YES ....NO

– the periods ceased by themselves ....YES ....NO

– other (please specify) .....

The last questions concern the use of "the pill".

---

7. Did you ever use "the pill"? Check the right answer.

....YES ....NO

(If you answered NO to this question, you can proceed to question 10)

8. If YES, why did you use "the pill"? Check the right answer, more than one answer is possible.

– to prevent pregnancy ....YES ....NO

– for painful periods ....YES ....NO

– for irregular periods ....YES ....NO

– other (please specify) .....

9. Could you indicate, as precisely as possible, those periods in your life in which you used "the pill" without interruption?
State month and year, for example: FROM March 1973 UNTIL September 1975.

	FROM		UNTIL	
	Month	Year	Month	Year
1.	.....	....	.....	....
2.	.....	....	.....	....
3.	.....	....	.....	....
4.	.....	....	.....	....
5.	.....	....	.....	....
6.	.....	....	.....	....

10. If you have NEVER taken "the pill", was this because you: (more than one answer possible)

– used no contraceptives ....YES N0

– used other methods to prevent pregnancies ....YES N0

– wished to become pregnant ....YES N0

– other (please specify): .....

11. This space is for your remarks and questions about this questionnaire.

Please mail the completed questionnaire in the enclosed brown return envelope, which does NOT need a stamp, to Prof. dr. H.A. Valkenburg, Institute of Epidemiology, Erasmus University Rotterdam.

THANK YOU FOR YOUR COOPERATION.

APPENDIX E
DUTCH REMINDER

REUMATOLOGIE
Dr. J. J. M. FESTEN-Dr. J. J. RASKER
Ziekenhuis De Stadsmaten Enschede
tel. 053-855 855

7511 JX Enschede, Dec. 1981
Ariënsplein 1, Tel. 053-85 34 75

Consult volgens afspraak

Geachte Mevrouw,

Enige weken geleden vroegen wij om uw medewerking bij een onderzoek naar het gebruik van "de pil" en het optreden van gewrichtsklachten. Van een klein aantal vrouwen hebben wij nog geen vragenlijst teruggekregen. Wellicht hebben sommige vrouwen niet geantwoord omdat ze "de pil" nooit of alléén maar vroeger hebben gebruikt, ofwel omdat het lang geleden is dat ze gewrichtsklachten hadden. Ook in al deze gevallen zouden wij graag uw antwoord ontvangen. Voor dit onderzoek zijn immers alle antwoorden even belangrijk.

Mogen wij u dan ook vragen, zo u dat nog niet heeft gedaan, om de vragenlijst alsnog in te vullen en op te sturen in de bruine antwoord-enveloppe waarop u GEEN postzegel hoeft te plakken. Voor het geval u de vragenlijst niet mocht hebben ontvangen, krijgt u hierbij een nieuwe vragenlijst met antwoord-enveloppe.

Wij danken u van hart voor uw medewerking. Na afloop van het onderzoek zullen wij u van de resultaten op de hoogte brengen.

Dr. J.J.M. Festen, reumatoloog.

APPENDIX F
TRANSLATION OF REMINDER

Dear Madam,

A few weeks ago, we asked you to cooperate in an investigation into the use of "the pill" and the occurrence of joint complaints. We have not yet received the completed questionnaire from a small number of women. Maybe some women did not answer because they never used "the pill" or because the joint complaints date from a long time ago. Whatever the reason, we would still like to receive your questionnaire. In this investigation *all* responses are equally important.

May we therefore ask you, if you have not already done so, to complete the questionnaire and mail it back in the brown return envelope which does NOT need a stamp. In case you did not receive the questionnaire of our first mailing, a new copy and return envelope have been enclosed.

We are grateful for your cooperation. At the end of the study, we will inform you as to the results.

Sincerely,

APPENDIX G
LOGISTIC REGRESSION ANALYSIS, EVER-USE

Detailed logistic regression analysis; all variables are 1/0 indicator variables.
Unstandardised coefficients and standard errrors. Analysis for Ever-use.

Variable	Relative to	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Constant	---	0.158(0.118)	-0.118(0.182)	0.959(0.388)	1.378(0.481)	1.498(0.489)	1.212(0.519)
Ever-use	Never-use	-1.020(0.184)	-1.150(0.193)	-0.744(0.209)	-0.725(0.210)	-0.715(0.211)	-0.866(0.220)
1930-34[1]	1926-29		0.092(0.260)	0.078(0.272)	0.079(0.273)	-0.007(0.279)	0.013(0.288)
35-39	26-29		0.472(0.279)	0.518(0.292)	0.515(0.293)	0.373(0.306)	0.361(0.313)
40-44	26-29		0.728(0.298)	0.724(0.312)	0.714(0.313)	0.569(0.327)	0.563(0.334)
45-49	26-29		0.635(0.349)	0.666(0.364)	0.678(0.364)	0.522(0.376)	0.470(0.384)
50-56	26-29		0.800(0.404)	0.917(0.417)	0.835(0.421)	0.649(0.436)	0.765(0.452)
1965-69[2]	1960-64			-0.569(0.446)	-0.566(0.447)	-0.532(0.447)	-0.600(0.457)
70-74	60-64			-0.856(0.426)	-0.848(0.427)	-0.770(0.430)	-0.756(0.440)
75-81	60-64			-1.792(0.406)	-1.812(0.408)	-1.684(0.414)	-1.620(0.424)
Married	Unmarried				-0.463(0.309)	-0.530(0.316)	-0.369(0.326)
Postmenop.	Premenop.					-0.538(0.349)	-0.656(0.357)
Utrecht[3]	Leiden						0.916(0.284)
Stadsm.	Leiden						-0.521(0.349)
Arnhem	Leiden						0.297(0.289)
Ziekenz.	Leiden						-0.150(0.317)
Log Likelihood		-346.195	-340.813	-321.256	-320.136	-318.895	-307.956

[1] year of birth
[2] year of first GP visit
[3] clinic

APPENDIX H

LOGISTIC REGRESSION ANALYSIS, EX- AND CURRENT-USE

Detailed logistic regression analysis. All variables are 1/0 indicator variables.
Unstandardised coefficients and standard errors. Analysis for ex- and current-use.

Variable	Relative to	Model 1	Model 2	Model 3	Model 4	Model 5	Model 6
Constant	---	0.158(0.118)	-0.105(0.183)	0.956(0.387)	1.379(0.481)	1.494(0.489)	1.214(0.518)
Ex-use	Never-use	-1.358(0.257)	-1.390(0.261)	-0.838(0.281)	-0.827(0.281)	-0.757(0.286)	-0.913(0.299)
Current-use	Never-use	-0.772(0.218)	-0.958(0.232)	-0.679(0.244)	-0.654(0.245)	-0.684(0.246)	-0.784(0.254)
1930-34[1]	1926-29		0.095(0.261)	0.081(0.273)	0.081(0.273)	-0.003(0.280)	0.024(0.289)
35-39	26-29		0.481(0.281)	0.521(0.293)	0.518(0.293)	0.379(0.308)	0.355(0.314)
40-44	26-29		0.664(0.301)	0.701(0.315)	0.689(0.316)	0.559(0.328)	0.545(0.334)
45-49	26-29		0.582(0.351)	0.647(0.366)	0.658(0.366)	0.518(0.376)	0.454(0.383)
50-56	26-29		0.709(0.407)	0.884(0.421)	0.797(0.426)	0.640(0.438)	0.735(0.453)
1965-69[2]	1960-64			-0.567(0.445)	-0.563(0.447)	-0.532(0.446)	-0.598(0.457)
70-74	60-64			-0.858(0.426)	-0.850(0.427)	-0.773(0.430)	-0.775(0.439)
75-81	60-64			-1.774(0.407)	-1.793(0.409)	-1.680(0.415)	-1.620(0.424)
Married	Unmarried				-0.468(0.309)	-0.530(0.316)	-0.371(0.325)
Postmenop.	Premenop.					-0.522(0.357)	-0.628(0.366)
Utrecht[3]	Leiden						0.910(0.284)
Stadsm.	Leiden						-0.584(0.349)
Arnhem	Leiden						0.278(0.289)
Ziekenz.	Leiden						-0.156(0.317)
Log Likelihood		-344.138	-339.779	-321.125	-319.982	-318.871	-308.183

[1] year of birth
[2] year of first GP visit
[3] clinic

APPENDIX I
DUTCH REPORT TO PARTICIPANTS

ERASMUS UNIVERSITEIT ROTTERDAM
Instituut Epidemiologie
Postbus 1738
3000 DR Rotterdam

Rotterdam, augustus 1982.

Geachte Mevrouw,

Enige maanden geleden nam U deel aan een onderzoek naar het verband tussen gewrichtsklachten en het gebruik van "de pil". Wij zijn U daarvoor zeer erkentelijk. Gaarne vertellen wij U in het kort wat dit onderzoek heeft opgeleverd.

Het onderzoek is uitgevoerd bij jonge vrouwen in vijf grote reumatologische poliklinieken in Nederland. In totaal namen er 724 vrouwen aan deel; dat is meer dan 85 per cent van degenen die wij hadden aangeschreven.

Het onderzoek heeft uitgewezen dat er geen enkele aanwijzing is, dat "de pil" reuma zou veroorzaken. Integendeel, het ziet er naar uit, dat vrouwen die "de pil" gebruiken een gedeeltelijke bescherming genieten tegen een bepaalde soort van reuma: het chronische reuma, meestal reumatoide arthritis genoemd. De bescherming die "de pil" zou bieden is zeker niet volledig: een vermindering van de kans op het ontstaan van reuma wil immers nog niet zeggen dat de ziekte helemaal niet meer kan optreden. Dat "de pil" een bescherming zou bieden tegen het ontstaan van dit soort reuma, is reeds verondersteld in engels en amerikaans onderzoek. Wij zijn blij dat dit dankzij Uw medewerking in Nederland is bevestigd. Wij zullen de resultaten van dit onderzoek dan ook naar voren brengen in binnen- en buitenlandse medische vakbladen.

Het onderzoek leert ons nog niet of het nuttig zou zijn om met "de pil" te beginnen als de reuma al is ontstaan.

Mocht U over het onderzoek zelf nog meer willen vernemen, dan kunt U ondergetekende telefonisch bereiken op het nummer 010-634463 van de Erasmus Universiteit.

Nogmaals hartelijk dank voor Uw medewerking,

J.P. Vandenbroucke, internist

mede namens:
J.W. Boersma, reumatoloog, Arnhem
Prof. dr. A. Cats, reumatoloog, Leiden
dr. J.J.M. Festen, reumatoloog, Enschede
A.P. Hartman, reumatoloog, Arnhem
O. Huber, reumatoloog, Utrecht
dr. J.J. Rasker, reumatoloog, Enschede
Prof. dr. H.A. Valkenburg, Rotterdam
dr. J. Weber, reumatoloog, Arnhem

APPENDIX F
TRANSLATION OF REPORT TO PARTICIPANTS

Dear Madam,

Some months ago, you participated in an investigation into the relation between joint complaints and the use of "the pill". We wish to thank you once again for doing so. We would like to tell you now what this study revealed.

For this investigation we approached young women attending one of five large rheumatology clinics in the Netherlands. In total, 724 women participated, which is more than 85 per cent of those who received a questionnaire.

The investigation has shown us that there is no indication that "the pill" could cause rheumatism. On the contrary, it looks as if women who use "the pill" receive some protection against one particular kind of rheumatism: chronic polyarthritis, usually called rheumatoid arthritis. The protection offered by "the pill" is certainly not complete: a diminished risk for a certain disease does not mean that the disease will never occur. The possibility that "the pill" would offer some protection against this type of rheumatism had already been indicated in British and North American investigations. Nevertheless, we are pleased to have been able to confirm this in the Netherlands, thanks to your cooperation. We will publish the results of this study in national and international medical journals.

The investigation does not yet answer the question of whether it would be beneficial to start taking "the pill" after the rheumatism has developed.
If you would like more information about this study, please phone the undersigned at the Erasmus University of Rotterdam (tel. number 010-634463).

Thank you again for your cooperation.
Sincerely,
J.P. Vandenbroucke, internist

also in the name of:
J.W. Boersma, rheumatologist, Arnhem
Prof. dr. A. Cats, rheumatologist, Leiden
dr. J.J.M. Festen, rheumatologist, Enschede
A.P. Hartman, rheumatologist, Arnhem
O. Huber, rheumatologist, Utrecht
dr. J.J. Rasker, rheumatologist, Enschede
Prof. dr. H.A. Valkenburg, Rotterdam
dr. J. Weber, rheumatologist, Arnhem

ABOUT THE AUTHOR

Jan Paul Vandenbroucke was born on March 8th, 1950, in Leuven. He attended primary and secondary school at the 'St.Pieterscollege' of the same city. He attended medical school from 1967 until 1974 at the University of Leuven. Together with the medical bachelor's degree, he obtained a bachelor's degree in philosophy, with emphasis on the philosophy of science.

In 1974 he started specialist training at the Department of Internal Medicine of the University of Leuven (Head: Prof. Dr. J. Vandenbroucke). Most of his time was spent in Intensive and Emergency Care (Prof. Dr. H. Delooz and Prof. Dr. R. Verberckmoes), Nephrology (Prof. Dr. P. Michielsen) and at the Outpatient Clinic (Dr. H. Bobbaers). During this training, he developed an interest in Epidemiology. The last year of his specialist training, 1978-79, was spent at the Harvard School of Public Health in Boston, Mass., where he obtained the Master of Science degree in Epidemiology. This stay was made possible by a Fulbright/Hays travel grant and the Frank Boas Scholarship of Harvard University. In 1979 he was certified as a specialist in Internal Medicine by the Belgian Ministry of Public Health.

In the fall of 1979, he moved to the Hague when he accepted the position of Head of the Department of Epidemiology of the Netherlands Heart Foundation (Medical Director: Dr. E. Dekker). In 1981 he joined the staff of the Institute of Epidemiology (Head: Prof. Dr. H.A. Valkenburg) at the Erasmus University Rotterdam and started the investigation described in this thesis. In 1982 he was appointed as part-time reader in Epidemiology at the Department of Environmental and Tropical Health Sciences (Head: Prof. Dr. K. Biersteker) of the Agricultural University of Wageningen.

He is a member of the Commission on Cardiac Surgery of the Dutch Health Council, and of the Scientific Board of the Dutch Thrombosis Federation. He married Christina Grauls, who obtained her medical degree at the University of Leuven in 1977 and is currently specialising in Medical Microbiology at the University of Utrecht. They have two daughters, Karianne and Myriam.