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RISK FACTORS FOR THE DEVELOPMENT OF CHRONIC RENAL FAILURE

**Epidemiological studies on the role of analgesic use,
occupational exposures
and socioeconomic background**

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SUMMARY

Chronic renal failure is a severe condition that reduces life expectancy and typically progresses to end-stage renal disease and a need for renal replacement therapy. In a large proportion of cases, chronic renal failure evolves from known renal or systemic diseases, but in some cases the pathogenesis remains unknown. The aim of this thesis was to investigate whether the use of paracetamol and aspirin, occupation and workplace exposures, and socio-economic status affect the development of chronic renal failure. We conducted a nation-wide population-based case-control study in Sweden. All 5.3 million native-born residents aged 18 to 74 years, living in the country during the period from May, 1996, through May, 1998, formed the study base. Personal interviews were performed with 926 patients with incident pre-uraemic chronic renal failure and 928 randomly selected control subjects.

Regular use of either paracetamol or aspirin in the absence of the other was associated with a significant increase by a factor of 2.5 in the risk of chronic renal failure from any cause. The relative risks rose with increasing cumulative lifetime doses, and were increased for most disease-specific types of chronic renal failure. The associations were only slightly attenuated when the recent use of analgesics, which could have occurred in response to antecedents of renal disease, was disregarded. Our results are consistent with the existence of exacerbating effects of paracetamol and aspirin on chronic renal failure.

Low socio-economic status was associated with an increased risk of chronic renal failure. In families with unskilled workers only, the risk of chronic renal failure was increased by 110% and 60% among women and men, respectively, relative to subjects living in families in which at least one member was a professional. Subjects with 9 years or less of schooling had a 30% higher risk compared with those with a university education. The excess risk was of similar magnitude regardless of underlying renal disease. The moderate excess was not explained by age, sex, body mass index, smoking, alcohol or analgesic intake. Thus, socio-economic status appeared to be an independent risk indicator for chronic renal failure in Sweden.

Our results did not support the hypothesis of an adverse effect of organic solvents on chronic renal failure development, in general. The overall risk for chronic renal failure among subjects ever exposed to organic solvents was virtually identical to that among never-exposed (odds ratio, 1.01; 95% CI, 0.81-1.25). No dose-response relationships were observed for lifetime cumulative solvent exposure, average dose, or exposure frequency or duration. The absence of association pertained to all subgroups of chronic renal failure. Detrimental effects from subclasses of solvents or on specific renal diseases cannot be ruled out.

Except for organic solvents and exhaust fumes, which were unrelated to risk of chronic renal failure, the exposure prevalence were low to the workplace exposure agents implicated in the literature. Silica and cadmium were associated with 39% (95% CI, 0-94%) and 26% (95% CI, -55-67%) excess risks, respectively, but apart from this, no striking excesses were found. There was an up to 2-fold variation in risk for chronic renal failure across occupational groups. This significant heterogeneity ($P=0.001$) in chronic renal failure risk among occupational groups could not be explained by studied lifestyle factors or workplace exposures.

To strive to seek, to find, and not to yield.

Joyce K. Kilmer, *Ulysses*

CONTENTS

List of papers	iv
Abbreviations and definitions	v
1 Introduction	1
2 Background.....	2
2.1 Risk factors for Chronic Renal Failure.....	3
2.1.1 Analgesics	4
2.1.2 Socio-economic status	8
2.1.3 Organic solvents	10
2.1.4 Heavy metals.....	11
2.1.5 Silica.....	12
2.1.6 Other risk factors	13
3 Aims.....	14
4 Methods	15
4.1 Setting.....	15
4.2 Study subjects.....	15
4.3 Collection of data	17
4.3.1 Lifetime exposure to analgesics	17
4.3.2 Measures of socio-economic status.....	19
4.3.3 Occupation and workplace exposures.....	19
4.4 Statistical analysis	20
4.4.1 Analysis of analgesic use (Paper I)	21
4.4.2 Analysis of socio-economic status (Paper II)	21
4.4.3 Analysis of solvent exposure (Paper III).....	21
4.4.4 Analysis of occupation and workplace exposures (Paper IV). 22	
5 Results.....	23
5.1 Results for chronic renal failure overall	27
5.1.1 Analgesics use (Paper I).....	27
5.1.2 Socio-economic status (Paper II)	29
5.1.3 Organic solvent exposure (Paper III)	30
5.1.4 Occupation and workplace exposures (Paper IV)	32
5.2 Results by underlying renal disease	35
5.2.1 Analgesics use (Paper I).....	35
5.2.2 Socio-economic status (Paper II)	36
5.2.3 Organic solvent exposure (Paper III)	38
5.2.4 Occupation and workplace exposures (Paper IV)	38
5.3 Results based on different periods of exposure.....	39
5.3.1 Analgesics use (Paper I).....	39
5.3.2 Organic solvent exposure (Paper III)	40
6 Discussion.....	41
6.1 Methodological considerations.....	41
6.1.1 Study design.....	41
6.1.2 Validity.....	42

6.1.3	Precision	44
6.2	Findings and implications	46
6.2.1	Paracetamol and aspirin use (Paper I)	46
6.2.2	Low socio-economic status (Paper II).....	47
6.2.3	Organic solvent exposure (Paper III)	48
6.2.4	Occupation and workplace exposures (Paper IV).....	49
6.3	Future research	51
	Conclusions	52
7	Acknowledgements	53
8	References.....	56

LIST OF PAPERS

- I. Fored CM, Ejerblad E, Lindblad P, Fryzek JP, Dickman PW, Signorello LB, Lipworth L, Elinder CG, Blot WJ, McLaughlin JK, Zack MM, Nyren O.
Acetaminophen, Aspirin, and Chronic Renal Failure.
New England Journal of Medicine, Vol. 345, No. 25, Dec. 2001, Pages 1801-1808

- II. Fored CM, Ejerblad E, Fryzek JP, Lambe M, Lindblad P, Nyren O, Elinder CG.
Socioeconomic status and chronic renal failure: a population-based case-control study in Sweden.
Nephrology Dialysis Transplantation, Vol. 18, No. 1, Jan. 2003, Pages 82-88

- III. Fored CM, Nise G, Ejerblad E, Fryzek JP, Lindblad P, McLaughlin JK, Elinder CG, Nyren O.
Absence of association between organic solvent exposure and risk of chronic renal failure: a nationwide population-based case-control study.
Submitted for publication

- IV. Fored CM, Nise G, Ejerblad E, Fryzek JP, McLaughlin JK, Elinder CG, Nyren O
Occupation, workplace exposures and risk of chronic renal failure.
In manuscript

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LIST OF ABBREVIATIONS AND DEFINITIONS

ADR	Adverse Drug Reaction
CI	Confidence Interval
CRF	Chronic Renal Failure
DDD	Defined Daily Doses
DPM	Days per month
e.g.	For example (<i>exempli gratia</i>)
GFR	Glomerular Filtration Rate
HE	Hygienic Effect
i.e.	That is (<i>id est</i>)
NUD	Without further description (<i>non ultra descriptus</i>)
NYK	Nordic Standard Classification of Occupations
OEL	Occupational Exposure Limit
OR	Odds Ratio
PCKD	Polycystic Kidney Disease
pmp	Per million people
SCB	Statistics Sweden
SEI	Swedish socio-economic classification
SE-SIC 92	Swedish Standard Industrial Classification 1992
SES	Socio-economic status
SoS	The Swedish Board of Health and Welfare
SRAU	The Swedish register of renal replacement therapy

Chronic renal failure	Denotes reduced glomerular filtration rate as a complication of parenchymal renal disease equivalent to “chronic renal insufficiency”.
End-stage renal disease	The stage when dialysis or kidney transplantation is necessary for the patient to survive.
The ORFAN-study	“ORFAN” is a Swedish acronym of “ O rsaker och R isk F aktorer för kronisk N jursvikt” (causes and risk factors for chronic renal failure), the name assigned to the large nationwide case-control study in which the studies in this thesis are parts.
Pre-uraemic	Renal failure in a stage without the need for renal replacement therapy
Renal replacement therapy	Dialysis or kidney transplantation. Treatments that, to a various degree, replace part of the kidneys’ functions.
Uraemia	Equivalent to end-stage renal disease

1 INTRODUCTION

In a large proportion of cases, chronic renal failure evolves from known renal or systemic diseases, but in some cases the pathogenesis remains unknown. Certain factors seem to promote chronic renal failure development irrespective of the underlying pathology; hypertension, proteinuria, high protein intake, smoking, heavy use of non-narcotic analgesics, and certain occupational exposures (Klag et al., 1996; Orth et al., 2000; Perneger et al., 1994; Ruggenti et al., 2001; Wedeen, 1997).

When renal adverse effects of non-narcotic analgesics first was discovered, workers at the Husqvarna Company had the habit of taking a few “stimulating” powders of phenacetin to keep up the output of work and to increase earnings (Grimlund, 1963). Women working at Swiss watch-making factories also were identified as excessive users of analgesics and had an increased incidence of renal injury (Dubach et al., 1968). Apart from this work-related heavy use of nephrotoxic analgesics, several chemical substances used primarily in the workplace have documented detrimental effects on the kidneys. Long-term exposure to heavy metals is injurious to the kidneys (Wedeen, 1997) and cadmium appears to influence the development of end-stage renal disease (Hellstrom et al., 2001). Exposure to organic solvents has long been suggested to cause and exacerbate renal disease (de Broe et al., 1996), in particular glomerulonephritis. A gradient by socio-economic status has been observed in a wide range of diseases, consistently favouring those of higher socio-economic status (Adler & Ostrove, 1999), but the evidence regarding renal disease is scant. Most of the effects of socio-economic status on disease risks in general have traditionally been attributed to lifestyle and occupational exposures with known biological effects.

Several of the previous investigations of the associations between analgesics use, workplace exposures or socio-economic status, and renal disease have been criticised because of methodological shortcomings (Hotz, 1994; McLaughlin et al., 1998). The last word has not been said regarding these possible risk factors for the development of chronic renal failure. To shed further light on these matters, we performed a nationwide, population-based, case-control study of pre-uremic chronic renal failure in Sweden. The methods of this study and the findings are presented in this thesis. In the design of this study and in the analyses, we tried to avoid the shortcomings of the previous investigations.

2 BACKGROUND

Chronic renal failure is a severe condition that reduces life expectancy. Most chronic nephropathies lack a specific treatment and once there is sufficient damage to the kidney, progression towards end-stage renal disease follows an inexorable and insidious course, almost without exceptions and irrespective of the cause of renal failure (Fink et al., 2001). The glomerular filtration rate is the best measure of overall kidney function. In clinical practice, the glomerular filtration rate is usually estimated from the creatinine clearance or serum creatinine level. The normal level of the glomerular filtration rate in young adults (age, 20 to 30 years) is approximately 125 ml/min and declines by approximately 1 ml/min per year thereafter (Levey, 2002). Chronic renal failure is defined as kidney damage or glomerular filtration rate less than 60 ml/min for three months or more (NKF K/DOQI guidelines, 2002). At this stage the renal failure is detectable by an elevated level of serum creatinine. The serum creatinine, however, is a poor predictor of glomerular filtration rate, as it may be influenced in unpredictable ways by assay techniques, renal tubular handling of creatinine, and factors such as: age, sex, body weight, muscle mass, diet and drugs (Parmar, 2002). In patients with chronic renal disease, the development of chronic renal failure and further progression towards end-stage renal disease show considerable variation between patients and by renal disease diagnosis.

Since 1958, it has been possible to perform long term haemodialysis. The first renal transplant was performed in 1954, but with the use of cadaver kidneys which began in 1959 and in 1962, with the introduction of azathioprine, the first immunosuppressive drug, kidney transplantation has evolved as the superior treatment option. Unfortunately, the frequency of transplantations is limited by a general shortage of kidneys donated. The introduction of long term peritoneal dialysis occurred later and a widespread adoption of this technique began with the development of continuous ambulatory peritoneal dialysis. In 1995, within the European Union, the overall annual incidence of patients with end-stage renal disease starting renal replacement therapy was 120 per million people. The corresponding rate was much higher in the U.S. (262 p.m.p./year) and in Japan (210 p.m.p./year), but lower in Canada (104 p.m.p./year) (Berthoux et al., 1999). The prevalence of end-stage renal disease requiring treatment varies internationally from 600 to 1,300 per million and is increasing steadily in most countries, with an estimated annual increase of 5 to 8%. In the U.S., in the year of 2000, the prevalence was 1,311 per million (USRDS, 2002). In Sweden, since 1991, every person with end-stage renal disease starting renal replacement therapy is reported to the Swedish register of renal replacement therapy – SRAU (The Swedish National Board of Health and Welfare, 2002). The annual incidence of renal replacement therapy in Sweden has been around 125 per million during the last years. By the end of the year 2001, the prevalence was 735 per million: 6,552 patients were on treatment, of which 3,440 (53%) had a well-functioning kidney transplant, 2,332 (36%) were treated with haemodialysis, and 735 (11%) with peritoneal dialysis (SRAU, 2002). The mean age among the prevalent patients was 56 years and 63% were men. The mean age among patients at the start of renal replacement therapy in Sweden has been gradually increasing during the last 10

years. In the last report (SRAU, 2002), men were on average 64 years old while the mean age among women were 62 years.

Glomerulonephritis is the most common renal disease diagnosis among patients on renal replacement therapy in Sweden despite the large inflow to the register of reports n patients with diabetic nephropathy starting treatment, diabetic nephropathy being the most common diagnosis among incident patients (Table 1) (SRAU, 2002).

Table 1. Proportions of patients receiving renal replacement therapy (prevalent patients) or starting treatment (incident patients) by diagnosis group in Sweden, 2001.*

	Proportion among incident patients	Proportion among prevalent patients
Glomerulonephritis	15%	28%
Diabetic nephropathy	26%	19%
Other renal diagnoses	20%	16%
PCKD [†]	7%	13%
Nephrosclerosis	18%	9%
Pyelonephritis	4%	9%
Uraemia NUD	10%	6%

* Data from SRAU-report 2002 (SRAU, 2002)

[†] Polycystic kidney disease

Prevention of end-stage renal failure is the main goal of nephrology owing to the high morbidity and mortality form dialysis and transplantation. In Sweden, the overall 5-year survival rate for patients on renal replacement therapy is 40%. For patients on dialysis, the 5-year survival is 23%, whereas the survival among patients with a functioning kidney transplant is 86%. The survival among patients on dialysis varies with age: the 5-years survival is 14% and 68% among patients older than 65 years and between 15 and 40 years, respectively.

2.1 RISK FACTORS FOR CHRONIC RENAL FAILURE

In a strict sense, any factor that irreversibly limits the kidneys' ability to satisfactory perform their tasks, is a risk factor for the development of chronic renal failure. Then, of course, renal disease is the most important risk factor, but any condition accompanied by a permanently insufficient renal blood flow (e.g., severe heart failure), or urinary outlet obstruction (e.g., pelvic tumour) is a risk factor for chronic renal failure. To simplify, risk factors for chronic renal failure are regarded as the factors associated with renal injury or renal disease.

The development of chronic renal failure requires the joint action of several component factors (Figure 1) (Rothman, 2002). Multiple aetiological factors throughout an individual's life, possibly including a genetic predisposition, congenital factors, and childhood and adult influences, determine the patterns of chronic renal failure incidence.

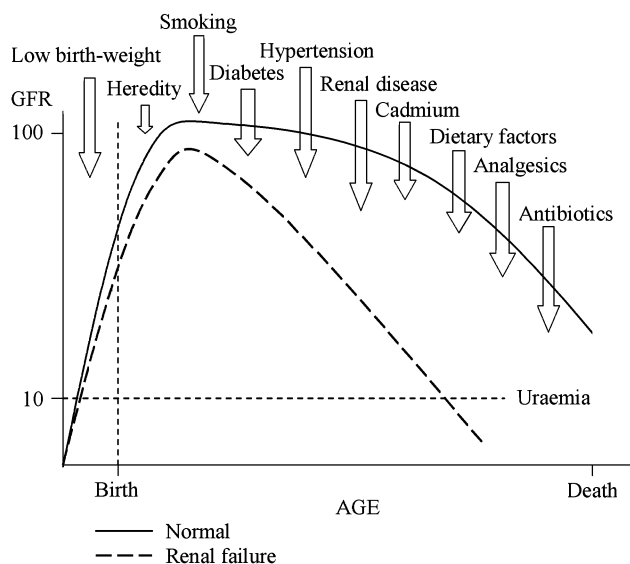


Figure 1. Schematic picture of possible component factors causing a decline in renal function (glomerular filtration rate – GFR).

Aging is a factor that plays a causal role in a large proportion of cases. A decreased glomerular filtration rate in the elderly is often considered to be normal for age but is associated with an increased risk of drug-induced toxicity or an increased vulnerability to other possible components causes (Rothman, 2002). In addition, the age-related decline in kidney function may contribute to the rising incidence of kidney failure (Levey, 2002). Hypertension occupies a place apart; most chronic renal failure patients are hypertensive, either because hypertension caused their kidney disease or because progressive renal insufficiency induced secondary hypertension.

2.1.1 Analgesics

Paracetamol (acetaminophen) and phenacetin are both derivatives of acetanilide (Figure 2) which, in the 1880s, by coincidence was found to possess antipyretic as well as analgesic activity. However, it was soon found to have unacceptable toxic effects (i.e., methaemoglobinaemia) prompting the search for less toxic derivatives. Paracetamol was discarded and phenacetin was introduced into clinical use in 1887 because of the latter's supposedly better toxicity profile (Clissold, 1986). Aspirin (acetylsalicylic acid) was marketed in 1899 as a salicylate analgesic that would not give rise to the adverse effects (i.e., gastric irritation, nausea, or tinnitus) frequently associated with sodium salicylate (Sneider, 2000).

Soon it was discovered that particular mixtures of phenacetin were not only effective for just pain relief, but also seemed to work as tonics and general panaceas (Drukker et al., 1986). The abuse of non-narcotic analgesics was first recognized in Australia in 1907, when it was noted that “what the drink habit is among men in Australia, the headache powder is among women” (Nanra et al., 1978).

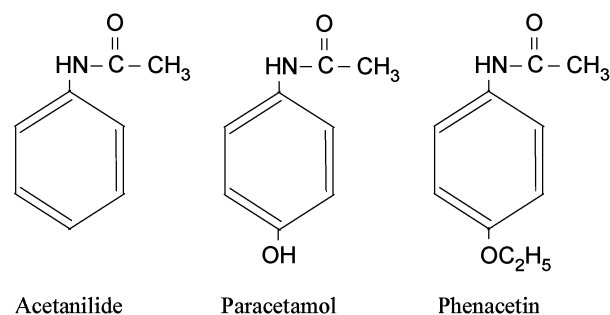


Figure 2. Structural formulae of acetanilide, paracetamol and phenacetin.

In Europe, an epidemic of analgesic abuse originated during the Spanish influenza pandemic of 1918-1919 in the small town of Huskvarna, Sweden (Grimlund, 1963). To alleviate the often intensive muscle pains from the influenza, the much liked and respected physician working in the town; Dr. Hjorton, prescribed a compound consisting of caffeine, phenacetin and phenazone. The mortality among those affected by the pandemic was high, but the survivors felt invigorated and recovering during convalescence on “Hjorton’s powder”. Even in good and normal health, it was discovered, the powder increased the feeling of strength and fitness. Taking a few “stimulating” powders throughout the working day became a habit at the factory of the Husqvarna Company, to keep up the output of work and to increase earnings. Since Hjorton’s powder could be obtained over-the-counter, without restraints, the increasing consumption of the powder went largely unnoticed by the medical profession. Many families could not think of beginning the day without the magic powder of Hjorton. It even became common in the community to offer a box of powders as a present.

The analgesic habit spread throughout the town of Huskvarna, spread to the neighbouring town Jönköping, and gradually to other more distant areas in Sweden. The phenacetin consumption in Huskvarna reached its peak in the beginning of the 1950s. By then, decades past the abuse had originated the death rate from uraemia and the number of kidney patients had rose to such an extent that an investigation was initiated to evaluate the causes of death in the town for the 10-year period from 1952 to 1961. An association between the abuse of Hjorton’s powder and the development of renal disease was discovered (Grimlund, 1963).

In 1953, two Swiss investigators linked the syndrome of chronic interstitial nephritis with papillary necrosis to analgesic abuse (Spühler & Zollinger, 1953). Regular use of analgesics was found to be a common practice among women in Swiss watch-making factories, and those who had metabolites of phenacetin in the urine had a higher prevalence of haematuria, proteinuria and elevated serum creatinine (Dubach et al., 1968). The analgesic nephropathy syndrome (originally called phenacetin nephropathy) emerged as a new disease entity and attention was drawn to the rapidly increasing consumption of analgesics in many countries, in particular in Switzerland, Sweden, Denmark and Australia, where analgesic nephropathy was emerging as a major problem (Prescott, 1982). There have now been hundreds of reports involving several thousand

patients from many countries worldwide, and analgesic nephropathy continues to be a serious problem in several countries, especially among elderly people (Buckalew Jr, 1996). In the early 1990s, the incidence of analgesic nephropathy among patients receiving dialysis was estimated to be 0.8, 3 and 9%, respectively, in the U.S., Europe and Australia (Elseviers & De Broe, 1999).

Phenacetin was quickly singled out as the cause of analgesic nephropathy since it was the common denominator in several investigations. At the same time phenacetin attracted attention as a cause of anaemia, cyanosis and methaemoglobinaemia (Prescott, 1982), and of uroepithelial cancers (Bengtsson et al., 1978; McLaughlin et al., 1985). Consequently, the use of phenacetin was restricted, first in Scandinavia beginning in the early 1960s and later in most other countries where this substance was heavily used (Buckalew Jr, 1996). The virtual commercial demise of phenacetin was accompanied by a rapid rise in popularity of paracetamol that was substituted for phenacetin in many popular analgesic mixtures (Matzke, 1997). Studies had shown that paracetamol was the major metabolite of phenacetin and, importantly, methaemoglobinaemia was caused by a different metabolite. In addition, paracetamol did not have the propensity to produce the central psychotropic effects of phenacetin (Clissold, 1986). In Sweden during the last decade, the sale of paracetamol has increased from 47 million to more than 130 million defined daily doses per year (DDD paracetamol = 3 grams) (Bergman & Sjoberg, 1995).

The mechanisms of analgesic nephropathy are unknown. Prostaglandin inhibition, negative effects on renal blood flow, toxic cellular injury, and free radical formation, are mechanisms proposed to explain the pathophysiology of experimental papillary necrosis from non-narcotic analgesics in general (Sabatini, 1996). Phenacetin was invariably taken in combinations with other analgesics of which the nephrotoxic potential is similar to that of phenacetin and may even be greater. Serious doubt was cast on the supposed role of phenacetin as the major aetiological agent in analgesic nephropathy (Prescott, 1982). The observation that an isolated ban on phenacetin had failed to control the epidemic of analgesic nephropathy in Australia and Belgium, whereas a ban on all mixed analgesics in Sweden and later in Australia seemed more successful, together with the results of epidemiological studies, indicated a causal role of analgesic mixtures in general. Consequently, in 1996, the ad hoc committee of the National Kidney Foundation in the U.S. (Henrich et al., 1996), as well as a group of European scientists who were experienced in this field (De Broe et al., 1996), stated that analgesic nephropathy is caused by the excessive use of different kinds of analgesic preparations containing two analgesic components combined with caffeine and/or codeine (Elseviers & De Broe, 1999). Later, however, it was shown that the decrease in analgesic nephropathy frequency among dialysis patients was similar in Belgium and Australia, despite the decrease of phenacetin consumption in Belgium was largely compensated by an increase in the consumption of mixed analgesics without phenacetin (Michielsen & Schepper, 2001).

In all but one (McCredie & Stewart, 1988) of the seven case-control studies referred to by the committee, the study population includes patients with end-stage renal disease or chronic renal failure of all causes and not exclusively analgesic nephropathy (Morlans et al., 1990; Murray et al., 1983; Perneger et al., 1994; Pommer et al., 1989; Sandler et al., 1989; Steenland et al., 1990). In clinical practice, a specific diagnosis of analgesic

nephropathy is almost never accompanied by histological evidence and is usually based on information about exposure before or in the early stages of the disease (Feinstein et al., 2000). Furthermore, findings from these studies should be interpreted with caution because of a number of inherent limitations and potential biases in the study design and data collection procedures (McLaughlin et al., 1998). These limitations include: failure to identify patients early enough in the natural history of their disease to collect reliable information on analgesic use at an aetiologically relevant time period; selection bias due to incomplete identification of subjects or low response rates; selection of cases and controls from different population bases; failure to employ survey techniques to improve reliability of recall of analgesic use; failure to collect detailed information on analgesic use such as year started and ended and reasons for switching analgesics; lack of standardization in the definition of regular analgesic use; and failure to adjust for phenacetin use and other confounding factors when assessing associations with analgesics other than those containing phenacetin (McLaughlin et al., 1998).

Still, the strongest and most consistent results pertain to phenacetin-containing drugs. The considerable body of clinical evidence point to a causal relationship between phenacetin use and renal disease. It is not clarified whether the nephrotoxicity of phenacetin-containing drugs in humans was due to users having taken high doses, to the fact that phenacetin was co-formulated with other constituents, or to the possibility that phenacetin itself was uniquely nephrotoxic (Delzell & Shapiro, 1998). The primary question today is whether the modern, non-phenacetin-containing analgesics are also associated with chronic renal disease in general or analgesic nephropathy or whether any apparent associations are caused by past use of phenacetin (Feinstein et al., 2000). Some three years ago, the Federal Drug Authorities of Germany, Austria, and Switzerland asked for a special ad hoc review of the available literature and evidence. The committee found no convincing evidence to confirm or refute the hypothesis that non-phenacetin combined analgesics are more nephrotoxic than single formulations, and concluded that sufficient evidence is absent to associate non-phenacetin combined analgesics with nephropathy (Feinstein et al., 2000).

A recently published study, conducted in the Physicians' Health Study cohort, revealed no positive association between analgesic use and the risk of moderate renal dysfunction; in fact, acetaminophen use appeared to be slightly protective (Rexrode et al., 2001). That study may have reduced the possibility of recall bias by ascertaining information about exposure to analgesics before renal dysfunction was diagnosed. Nonetheless, its results must be interpreted cautiously. The level of exposure to analgesics was ascertained retrospectively after a follow-up period of 14 years, and serum creatinine testing was performed no longer than 1 to 2 years after the assessment of exposure and involved only half of the initial cohort. Subjects with renal or systemic disease were unlikely to be recruited into the Physicians' Health Study or to remain in the study until the end of follow-up. The results may support the finding that persons without pre-existing disease who use analgesics have only a small risk of end-stage renal disease.

In another related and recently published study, conducted in the Nurses' Health Study II cohort, the use of NSAIDs and use of acetaminophen (paracetamol) were significantly associated with increased risk of hypertension, but aspirin was not (Curhan et al., 2002). The relative risk of hypertension for women taking NSAIDs 22 days or more per month

was 1.86 (95% CI, 1.51-2.28) and for those taking paracetamol was 2.00 (95% CI, 1.52-2.26). A substantial proportion of hypertension and the associated morbidity (including chronic renal disease) may be due to the use of these medications.

2.1.2 Socio-economic status

A gradient by socio-economic status has been observed in a wide range of diseases (Adler & Ostrove, 1999). Socio-economic status represents an important risk indicator for cardiovascular disease (Kaplan & Keil, 1993), but evidence linking low socio-economic status to renal disease is scant. To my knowledge, the influence of socio-economic status on chronic renal failure before the end-stage has not previously been examined. The association between socio-economic status and the incidence of treated end-stage renal disease has, however, been examined in a few previous studies. In a study on the incidence of end-stage renal disease in New York State using an area-based index of socio-economic status derived from income, occupational and educational data, a relationship between socio-economic status and end-stage renal disease was found in Caucasian Americans but not in African Americans (Byrne et al., 1994). A study comprising the entire United States examined the relationship, by county of residence, between the incidence of end-stage renal disease and average per capita income. The results showed an approximately 60% higher incidence of end-stage renal disease in the lowest income category compared to the highest, and no racial differences were seen (Young et al., 1994). Similar gradients across different ethnicity were also found in a population-based case-control study of patients commencing end-stage renal disease treatment in Maryland, Virginia, West Virginia and Washington DC. In this study, the adjusted risk for the development of end-stage renal disease was 4.5 times higher in the lowest income category compared to the highest (Perneger et al., 1995b). No difference in socio-economic status between patients starting renal replacement therapy and general population was found in a recent survey in Scotland (Metcalf et al., 1999).

The magnitude of the associations found in the previous studies using income as a measure of socio-economic status may be questioned. The income-earning capacity is often reduced among end-stage renal disease patients and low income may be a consequence, rather than a cause, of end-stage renal disease. Furthermore, African Americans and American Indians have been reported to have at least a 4-fold greater incidence of end-stage renal disease than white Americans (Powers & Wallin, 1998), and indigenous Australians constitute less than 2% of the Australian population, but represents almost 10% of new patients commencing treatment for end-stage renal disease (Cass et al., 2002). Accordingly, the associations found may be the result of joint effects of both race and socio-economic status.

We still have very little understanding of how aspects of socio-economic status may operate in conjunction with ethnicity to influence health (Adler & Ostrove, 1999). In research on differences of incidence of end-stage renal disease according to ethnicity, the focus has been on racial differences in physiological and pathological responses. In the American Multiple Risk Factor Intervention Trial (MRFIT), disparities in socio-economic status, as well as in blood pressure, were found to relate importantly to the excess risk of end-stage renal disease in African American men compared with white men (Klag et al., 1997). In a recent ecological study confined to indigenous Australians,

socio-economic factors appeared to be strongly associated with rates of end-stage renal disease. Indigenous Australians ranked in the highest quartile of disadvantage had a standardized incidence of end-stage renal disease 7.8 times higher than that for indigenous Australians ranked in the lowest quartile, and 18.5 times higher than that for all Australians (Cass et al., 2002).

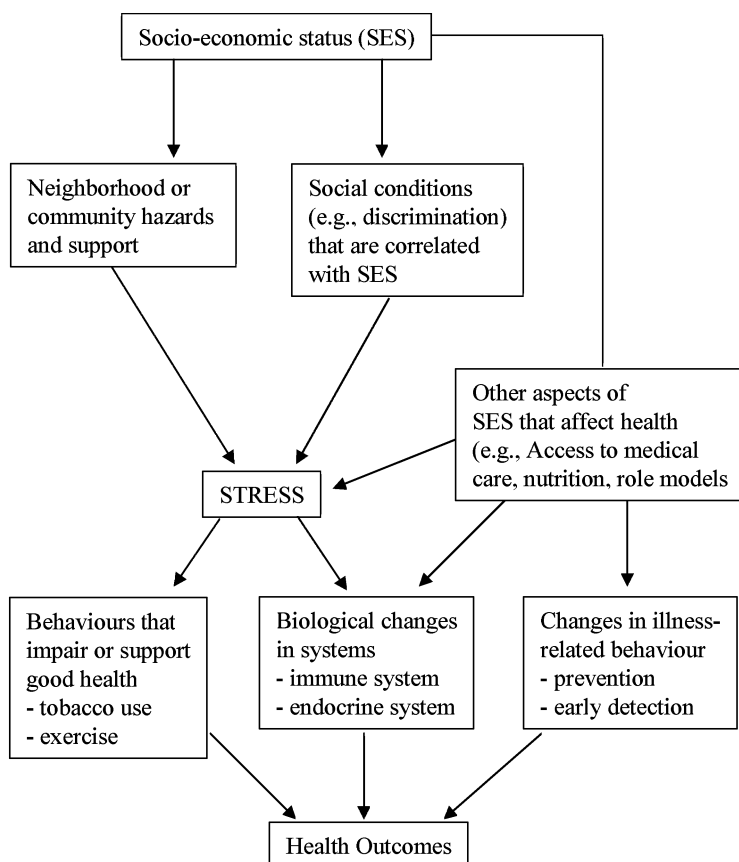


Figure 3. Model for the pathways by which socio-economic status may affect health [from (Baum et al., 1999)]

A number of variables have been suggested as moderators of the relationships between socio-economic status and health outcomes, including the enabling effects of higher socio-economic status, ethnicity, access to medical care, residential environments, health behaviours, and workplace exposures. Many of the toxic ingredients in the mix of variables that contribute to or are associated with lower socio-economic status have, however, not been identified (Baum et al., 1999). Accumulating evidence suggests that social status itself may confer health benefits possibly via psychosocial mechanisms (Fitzpatrick, 2001). Chronic stress has been proposed as the mediator of the socio-economic status – health relationship (Baum et al., 1999; Levi et al., 2000), excess chronic stress burden possibly interfering with health maintenance, affect response to acute stressors, and influence survival and well being (Figure 3).

2.1.3 Organic solvents

Organic solvents include hydrocarbons, glycols (e.g., ethylene glycol, dioxane glycerol), solvents of abuse (e.g., toluene, xylene), and chemicals used in various industrial processes and household activities (de Broe et al., 1996). Chronic health effects in solvent-exposed individuals have been a concern in occupational medicine for more than two decades. Initial study results have led to terms such as “Scandinavian solvent syndrome”, which refer primarily to nervous system disorders (Hogstedt, 1994). As a result of the research, policies and programs were developed throughout the world to control excessive exposure to solvents. Substitution of non-solvent-containing products for those containing solvents has occurred, and if substitution of a less toxic product was difficult, exposure control through appropriate occupational hygiene measures has been accomplished (Baker, 1994).

Exposure to organic solvents has long been suggested to cause and exacerbate renal disease (de Broe et al., 1996). Support for this association comes from several case reports, cross-sectional and case-control studies (Hotz, 1994). A majority of these studies, however, suffer from small sample size, imperfect exposure assessment, equivocal case definition, inappropriate control groups, and lack of information on important co-variables (Churchill et al., 1983; de Broe et al., 1996; Hotz, 1994). In addition, most previous case-control studies were limited to various glomerulopathies, and the role of organic solvents in the development of other nephropathies remains unclear. Experiments in animals have shown that solvent exposure leads to renal tubular damage (Nelson et al., 1990). Changes in urine sediment associated with tubular damage have also been reported in humans (Hotz et al., 1989), the long-term significance of these findings being uncertain. Heavy exposure to organic solvents has, in case reports, been described among patients with Goodpasture’s syndrome, a rapidly progressive autoimmune renal disease also involving alveoli of the lungs (Wedeen, 1997). A biologic mechanism has been postulated regarding the association with glomerulonephritis: antiglomerular basement membrane antibody related to release of antigen after solvent exposure (Baker, 1994).

As to the association with glomerulonephritis, in a recent report (Ravnskov, 2000b), a meta-analysis was performed using the published data from 14 out of the 18 case-control studies present on this matter. The author argues that there is much evidence of organic solvent exposure worsening renal function in glomerulonephritis. The heterogeneous design among the 14 case-control studies included in the analysis and the methodological limitations of several of the included studies, however, preclude firm conclusions. Moreover, most evidence weighed against any important role of solvent exposure in the strongest study published so far (Asal et al., 1996), and no overall relationship was observed between solvent exposure and histologically well-defined primary glomerulonephritis in another carefully designed study (Stengel et al., 1995), although heavily exposed male patients admittedly had an excess risk.

The only previous study of patients with chronic renal failure regardless of underlying disease showed no more than a weak and statistically non-significant association with solvents overall (Nuyts et al., 1995). In this study, exposure to the solvent sub-class

“oxygenated hydrocarbons” was however, associated with a five-fold increase in risk, but the confidence interval was wide and no dose-response relation could be demonstrated. In one previous study, a significantly greater exposure to organic solvents has been shown among patients with insulin-dependent diabetes and with diabetic nephropathy, as compared with patients with diabetes but without nephropathy (Yaqoob et al., 1994b).

2.1.4 Heavy metals

Exposure to cadmium is implicated in a number of clinical complications, primarily renal dysfunction and bone disease, but also in cancer of the lung and prostate (Jarup et al., 1998). The kidneys are considered to be the critical organ for cadmium toxicity and the nephrotoxic effect of heavy cadmium exposure is well established (Friberg et al., 1986), but even at very low levels of exposure, this heavy metal can cause kidney damage (Jarup et al., 2000). Battery factories, zinc smelters, pigment plants and soldering activities cause occupational exposure to cadmium. The most significant contemporary source results from the production of nickel-cadmium batteries (Jarup, 2002). The main route of cadmium exposure in the occupational setting is via the respiratory system. Environmentally, the main source of cadmium exposure is tobacco smoke for the smoker, followed by diet for the non-smoker (Jarup et al., 1998). Cadmium is easily available for up-take in grain, rice and vegetables, and there is a clear association between the cadmium concentration in soil and in the plants grown on that soil.

Cadmium induces tubular damage which in most cases is irreversible even if exposure ends (Jarup et al., 1998). The resulting tubular proteinuria does not give rise to any subjective symptoms or manifestations of disease (Wedeen & De Broe, 1998), and it may, from a health point of view, have limited importance. Glomerular damage with a decreased filtration rate may, however, also develop in occupationally exposed workers (Elinder, 2000), and end-stage renal disease has been reported in a few heavily exposed cadmium workers (WHO, 1992). The results of a recent study of people occupationally or environmentally exposed to cadmium showed that tubular proteinuria occurs in environmentally exposed people at lower concentrations of cumulative cadmium doses than was previously realised (Jarup et al., 2000). In addition, results indicating that relatively low levels of cadmium exposure may contribute to the development of chronic renal failure have been presented (Hellstrom et al., 2001).

High level occupational exposure to lead, or consumption of illicit alcohol adulterated with lead, has been linked to chronic renal failure, hypertension, hyperuricaemia, and gout (Wedeen, 1992). In children, heavy exposure to lead has been reported to cause renal interstitial damage and a reduced glomerular filtration (Loghman-Adham, 1997). The critical effect of lead is, however, primarily on the central nervous system. In addition, lead also inhibits enzymes crucial for the synthesis of haeme, anaemia being one of the serious effects of lead exposure. As a result many industrial sources of lead have been eliminated, and substantial reductions in the environmental sources of lead have been accomplished (Elinder, 2000). Still, low-level lead exposure is considered to be a public health problem (Loghman-Adham, 1997). Lead is accumulated in bone and the skeletal lead stores can be mobilized during both normal and increased bone turnover, e.g., during pregnancy, lactation, and at menopause (Berglund et al., 2000). A

multitude of studies have documented an association between chronic occupational lead exposure and impairment of renal function. Whether chronic lead nephropathy exists as a clinical entity has, however, been questioned (Nuyts et al., 1991). Many studies of occupational lead poisoning have not taken into account the co-exposure to other toxins such as cadmium. Several studies on workers with less severe occupational lead exposure have been performed in the recent years, but neither tubular nor glomerular damage could be demonstrated (Elinder, 2000; Loghman-Adham, 1997).

The toxicity of mercury depends on both its chemical form and the route of absorption. Elemental mercury is virtually harmless when ingested, but inhalation of the metallic vapour can produce bronchial damage and later neurological disease (Satoh, 2000). Once in the environment, elemental mercury undergoes biotransformation to both organic and inorganic salts that are absorbed by living organisms and thus enter the food chain. The organic methyl mercury is extremely toxic and readily adsorbed from the gastrointestinal tract of humans and animals. The highest levels of methyl mercury are found in predatory fish and sea mammals (WHO, 1990). Severe epidemics of methyl mercury poisoning have occurred in Iraq and in Japan (Minamata disease). Organic mercury primarily affects the central nervous system. Different types of renal effects are seen: acute renal failure, tubular and glomerular injury with nephrotic syndrome. The mercury-induced nephrotic syndrome most often disappears spontaneously after termination of exposure (Wedeen, 1997).

Massive exposure to chromium consistently causes acute tubular necrosis with a rapid onset of renal failure (Wedeen & Qian, 1991), yet chronic renal disease due to occupational or environmental exposure to this metal has only been reported once (Nuyts et al., 1995). The associations between chronic renal failure and several different occupational exposures were examined in this case-control study with subjects living in industrial areas in Belgium. Some previously less well-documented risk factors were defined, including chromium, copper and tin (Nuyts et al., 1995). The relevance of these findings is uncertain.

2.1.5 Silica

Silicon (Si) is the second most abundant element, constituting 28% of the earth's crust. Silicon does not occur naturally as a free element; it is found as silicon dioxide, the so-called silica, and in an enormous variety of silicates. With regard to silicon toxicity, most lesions are associated with occupational exposure to silicon compounds (e.g., miners, sandblasters, bricklayers, pottery workers), in which inhalation of the compounds has been associated with diseases of the lung (de Broe et al., 1996). Silica exposure in recent years has been associated with non-malignant renal disease, rheumatoid arthritis, and other autoimmune diseases (Parks et al., 1999). The epidemiological data are, however, conflicting and the mechanism by which silica causes kidney disease is unknown (Stratta et al., 2001). Immunologic injury to the glomerulus is proposed as a pathogenic mechanism, as are a direct nephrotoxic effect from silica (Rosenman et al., 2000). The findings in the literature that silica exposure is related to subsequent kidney disease were recently strongly supported by the results of a cohort-study of 4,626 silica-exposed workers in the sand industry (Steenland et al., 2001). A two-fold excess of end-stage renal disease overall was seen among silica exposed workers in comparison with the U.S.

incidence rates. This excess was greatest for glomerular disease. Internal exposure-response analyses showed a pronounced trend of increasing end-stage renal disease by increasing cumulative exposure (Steenland et al., 2001).

2.1.6 Other risk factors

Other risk factors for chronic renal failure or end-stage renal disease have not been well-described. In fact, epidemiology has contributed little to the understanding of kidney disease aetiology. In the past, the immediate need for therapy may have eclipsed the longer-term need to develop preventive strategies (Perneger et al., 1995a). Aside from a beneficial effect of protein restriction on the progression of chronic renal disease has been indicated in one study (Levey et al., 1999), there is to my knowledge, little research investigating other dietary factors in relation to chronic renal failure. While regular physical activity can reduce the risk of cardio-vascular disease, the effect of physical activity on renal disease development is unknown (Beto & Bansal, 1998).

In contrast, substantial evidence exists linking renal injury with smoking among patients with diabetic nephropathy, among patients with non-diabetic renal disease, and among patients without primary renal disease but at high renal risk (e.g., severe essential hypertension) (Orth, 2002). Recently, it was shown, in a large non-diabetic sample of the Dutch population (n=7,476), that the urinary albumin excretion rate is correlated with the number of cigarettes smoked (Pinto-Sietsma et al., 2000). Furthermore, in an Australian population-based cross-sectional study, smoking was associated with indicators of kidney damage in a randomly selected sample without hypertension or abnormal glucose metabolism (Briganti et al., 2002). In addition, smoking was associated with renal impairment in men and with proteinuria in those with systolic blood pressures or 2-hour glucose levels in the high-normal range. A dose-response effect on glomerular filtration rate and urine protein-creatinine ratio was shown with lifetime exposure to smoking (Briganti et al., 2002).

The consumption of more than two alcoholic drinks per day, on average, was associated with an increased risk of kidney failure in one previous case-control study (Perneger et al., 1999). In addition, the abuse of illicit substances may cause or exacerbate a wide spectrum of kidney diseases (Crowe et al., 2000).

3 AIMS

The aims of the studies included in this thesis are:

To evaluate the extent to which paracetamol and aspirin intake increases risk of chronic renal disease development.

To evaluate whether the risk of developing chronic renal failure varies with socio-economic status.

To evaluate the extent to which occupational exposure to organic solvents affects risk of chronic renal failure.

To evaluate the extent to which occupational exposure to exhaust fumes, non-organic and organic dusts, and metals affects risk of chronic renal failure, and to evaluate whether the risk varies with occupation.

And while doing so learning the methods of epidemiological research.

4 METHODS

4.1 SETTING

The nationwide population-based case-control study of chronic renal failure (The ORFAN study) that formed the base for this thesis was conducted in Sweden where exceptional opportunities for epidemiological research are offered (Calltorp et al., 1996). The most important feature that enabled us to perform this study was the national registration numbers assigned to all Swedish residents since 1947 (Lunde et al., 1980). The unique ten-digit number includes information about date of birth and sex and is used in the Swedish Population Register as well as in individual medical records. We used the national registration numbers to identify eligible case patients and to select controls within the same study base.

The Swedish Population Register is an excerpt from the national registration data kept at the taxation authorities. Besides the name and address, it includes citizenship and country of birth, information that we used in the definition of the study base. The continuously updated register provided a well-defined study base of all 5.3 million native Swedes, 18 to 74 years of age, who were resident in the country during the ascertainment period, May 20, 1996 through May 31, 1998.

Finally, the structure of the Swedish health care system with financially and administratively independent counties, each of which provides health care at hospitals and primary health care centres, at charges low enough to ensure equal access to public health care for all citizens (Calltorp et al., 1996), also facilitated the realization of this study.

4.2 STUDY SUBJECTS

Case patient ascertainment is outlined in Figure 4. Eligible patients were men whose serum creatinine level exceeded 300 μmol per litre (3.4 mg per decilitre) or women whose serum creatinine level exceeded 250 μmol per litre (2.8 mg per decilitre), for the first time and permanently. To ensure complete identification of all eligible patients, medical laboratories ($n=68$) covering practically all inpatient and outpatient care in Sweden provided monthly lists of all serum creatinine measurements performed. Physicians at each hospital ($n=60$) where patients with renal disease are treated determined patients' eligibility for the study by reviewing the medical records of patients with elevated serum creatinine levels. The diagnosis of the condition underlying renal failure was based on the results of routine clinical evaluation. Patients with chronic renal failure whose cause was prerenal (e.g., severe heart failure) or postrenal (i.e., obstruction of the urinary tract) and patients who had received kidney transplants were excluded. A second creatinine measurement, three months after the first, was obtained when the chronic nature of the renal failure was uncertain. To allow for day-to-day variation, the thresholds for eligibility with this second measurement were lower (250 μmol per litre for men and 200 μmol per litre [2.3 mg per decilitre] for women); patients with lower values were excluded from the study.

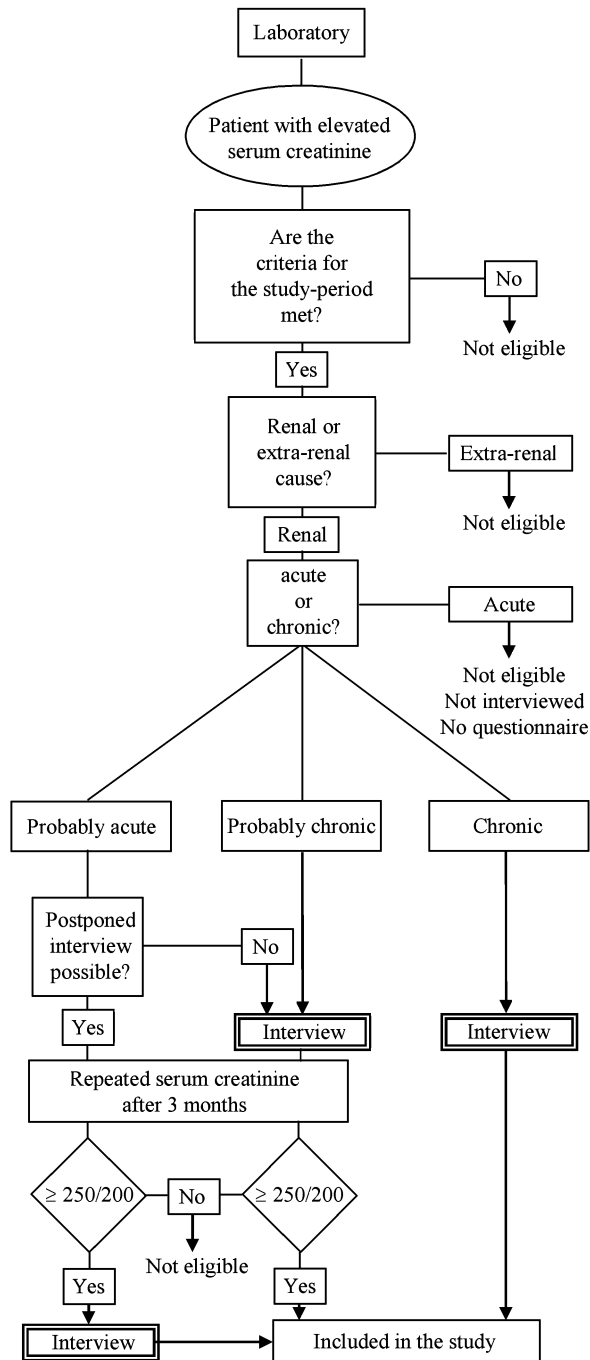


Figure 4. Case patient ascertainment.

The controls were randomly selected on three occasions throughout the ascertainment period from the Swedish Population Register (Calltorp et al., 1996) and were frequency-matched to the patients with renal failure according to age (in 10-year strata) and sex. All study subjects provided oral informed consent before being enrolled. The ethics committees of the participating centres and the Swedish Data Inspection Board approved the study protocol.

4.3 COLLECTION OF DATA

Each subject first received a mailed self-administered questionnaire inquiring about education, marital status, anthropometric measures, and personal lifestyle factors such as alcohol consumption, tobacco use, and diet. In a subsequent face-to-face interview information was obtained on occupational history and work-related exposures, physical activity, and medical history including a detailed history of lifetime use of non-narcotic analgesics. The professional interviewers from Statistics Sweden (SCB – Statistiska centralbyrån) also examined the mailed questionnaire to ensure completeness, and assisted the subjects in completing missing answers. Depending on the occupational history, selected subjects underwent an additional telephone interview performed by an occupational hygienist. This interview comprised detailed questions about workplace conditions and exposures. The interviewers could not be kept blinded to the case/control status of the participants, but they were unaware of the study hypotheses, and they were trained to interview all subjects in a strictly standardized manner. Interviews with patients with renal failure lasted an average of 80 minutes, and interviews with control subjects lasted an average of 70 minutes.

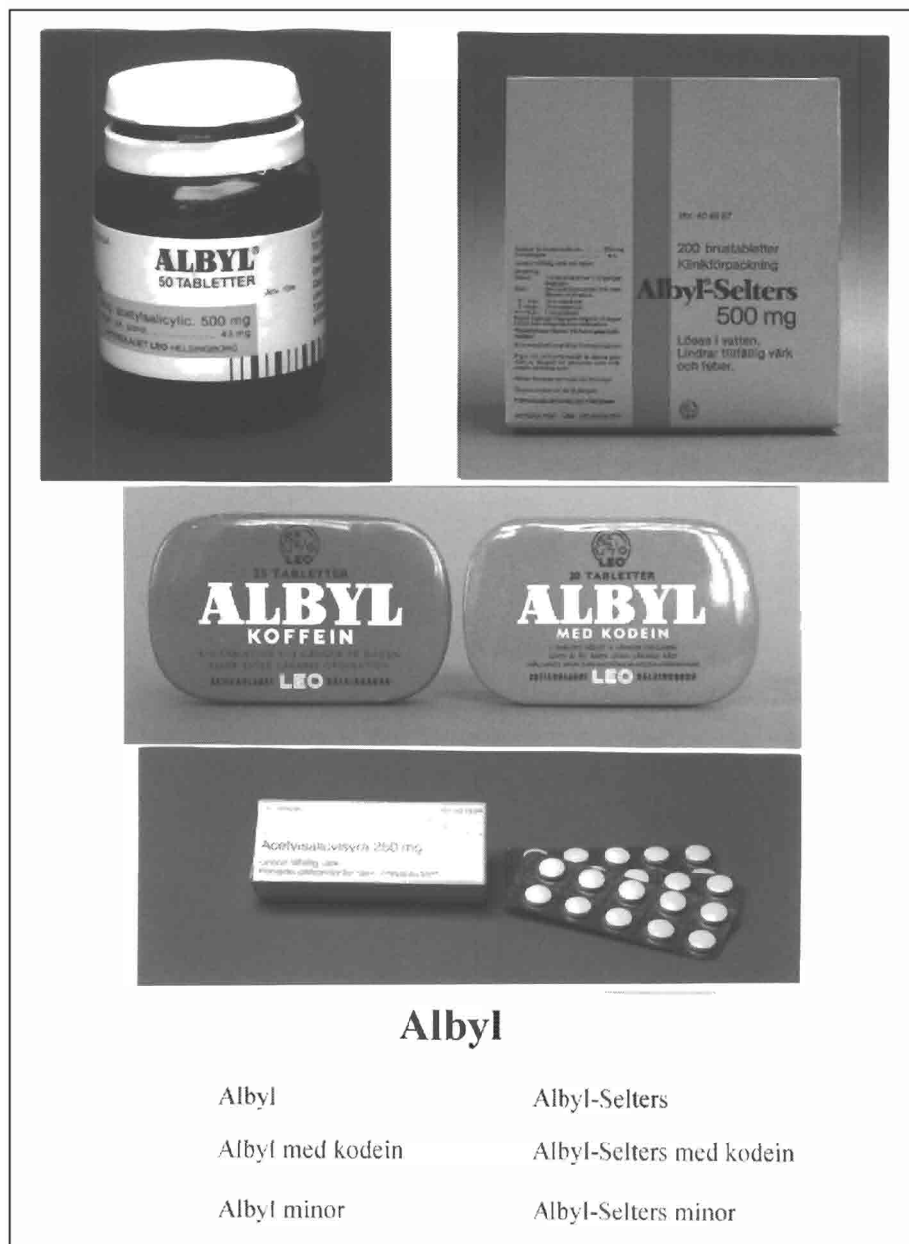
4.3.1 Lifetime exposure to analgesics

By searching the archives of the Swedish Medical Products Agency (Läkemedelsverket) we identified all analgesics that were on the Swedish market between 1960 and 1996. With the kind assistance of the historical department at the Swedish Academy of Pharmacy (Apotekarsocieteten) and of several pharmaceutical companies we produced a booklet that included colour pictures of the packaging of all analgesics containing paracetamol (acetaminophen) or phenacetin as well as the 78 most frequently sold major brands of the 174 other non-narcotic analgesics (Picture 1).

Each subject first reviewed the colour pictures and then reported their lifetime consumption of the brands of drugs that appeared in the booklet as well as their lifetime consumption of any other analgesics. The analgesics use information was registered during the interview using laptop computers. Multiple periods of use of each analgesic brand were allowed. Information about the consumption of brand-name drugs was converted to amounts of generic drug ingredients.

Regular use of an analgesic was defined as use at least twice a week for at least two months. All subjects were asked to report their age during each period of regular use, the duration of each period, and the dose used during that period. Subjects whose cumulative lifetime dose exceeded 20 tablets of an analgesic brand but who did not use it regularly were classified as sporadic users. Nonusers of an analgesic brand were defined as those who reported taking fewer than 20 tablets during their lifetime. Subjects also answered

questions about changes in their pattern of use and in the patterns of aches and pains prompting the use of analgesics.



Picture 1. The first page from the booklet used at the interviews with colour pictures of the packaging of analgesics.

4.3.2 Measures of socio-economic status

The mailed self-administered questionnaire included questions on years of education and highest educational degree, and information on every occupation held for more than a year was obtained during the face-to-face interviews. The socio-economic status associated with reported occupations was derived from the official Swedish socio-economic classification scheme (SEI, 1982). In addition, occupations of spouses and parents were recorded to assess “household socio-economic status”.

The occupation-based socio-economic scores were aggregated into the following classes: (i) unskilled and semiskilled manual workers, (ii) skilled manual workers, (iii) assistant non-manual employees, (iv) intermediate non-manual employees, and (v) employed or self-employed professionals, higher civil servants and executives. A sixth group of self-employed (other than professionals) and farmers was analyzed separately. Each subject was grouped according to the highest socio-economic score obtained from the occupational history. The spouse with the highest score determined the household socio-economic status. Students were classified according to the socio-economic status of their parents. Educational level was grouped into three categories based on the number of years of education (0-9, 10-12, 13 years or more).

4.3.3 Occupation and workplace exposures

The occupational history included company name, type of industry, occupational title, work tasks, and duration of each employment period of at least one year during the subject’s lifetime. Occupations were coded according to the Nordic Standard Classification of Occupations (NYK, 1990) and type of industry according to the Swedish Standard Industrial Classification (SE-SIC 92, 1992). For subjects reporting employment within several different occupational fields, the occupational field in which the subject reported the longest employment duration was classified as one of eight “main occupations”: (i) manufactory work, (ii) administrative, financial, and clerical work, (iii) technical, scientific, humanistic, and artistic work, (iv) health care and social work, (v) commercial work, (vi) service occupations, (vii) transport and communications work, and (viii) agricultural, forestry, and fishing industry work, corresponding to the occupational field classes in NYK. Any exposure to organic solvents, organic and non-organic dusts, heavy metals, and combustion exhaust fumes was recorded during the face-to-face interview, including exposure during employments lasting less than a year as well as leisure-time exposure. The exposure information included duration (years) and description of relevant work tasks and exposure frequency (days per month).

To evaluate exposure status and decide if additional information was needed, a senior industrial hygienist reviewed the occupational histories and the exposure information for every subject. Further detailed information on work tasks, equipment, duration and frequency of exposure, the general work environment, the ventilation system and use of personal protective equipment as well as any improvements in the work environment were pursued in an additional standardized telephone interview. We intended to keep the industrial hygienist assistant who performed the additional telephone-interviews blinded to the case/control status of the subjects, but experienced that this was impossible since some case patients revealed having a chronic renal disease during the interview.

For every employment period, the senior industrial hygienist estimated the intensity of exposure to: (i) organic solvents (e.g., aliphatic, acyclic, aromatic hydrocarbons, aldehydes, ketones, alcohols, glycols, glycol ethers, or mixtures of these compounds), (ii) organic dust (i.e., wood, grain, textile fibre, and cellulose dust), (iii) non-organic dust (i.e., silica and asbestos), (iv) metals (i.e., lead, mercury, chromium, cadmium, nickel, copper, tin, zinc, and aluminium), and (v) combustion exhaust fumes (i.e., motor exhaust and other products of combustion), using the expert rating method previously described (Siemiatycki et al., 1997).

Exposure intensity was classified on a four-level scale in terms of approximate additive Hygienic Effect (HE). For all substances except carbommonoxide (CO) and nitrogen dioxide (NO₂), exposure to a HE of 1.0 corresponds to an average exposure level during an 8-hour working day equal to the Occupational Exposure Limit prescribed by the Swedish Work Environment Authority in 1996 (OEL, 1996). The classes were: (i) “unexposed”, < 3% (1/30) of the OEL (implies no more than background level exposure), (ii) “low exposure”, ≥ 3 and < 10% (1/10) of the OEL, (iii) “intermediate exposure”, ≥ 10 and < 30% (1/3) of the OEL, and (iv) “high exposure”, ≥ 30% of the OEL. The corresponding classes of exposure to CO and NO₂ were: (i) “unexposed”; CO, < 1 parts per million (ppm); NO₂, < 0.03 ppm, (ii) “low exposure”; CO, ≥ 1 and < 3 ppm; NO₂, ≥ 0.03 and < 0.1 ppm, (iii) “intermediate exposure”; CO, ≥ 3 and < 10 ppm; NO₂, ≥ 0.1 and < 0.3 ppm, and (iv) “high exposure”; CO, ≥ 10 ppm; NO₂, ≥ 0.3 ppm.

Cumulative lifetime exposure for each substance was calculated as the product of the intensity (HE), exposure frequency (days per month, DPM), and the duration (years) of the exposure, summed over all employments in the subject’s occupational history. To investigate solvent exposure further, we used self-reported body weight at age 20 years to calculate lifetime-dose per kilogram (HE*DPM-years/kilogram) as an estimate of the biological dose delivered to the tissues. An average cumulative exposure during years of exposure was also calculated by dividing the lifetime-dose by the number of years exposed. Dose estimations of solvent exposure were categorized according to quartiles among exposed control subjects. The other occupational exposures were categorized according to tertiles among the exposed controls.

4.4 STATISTICAL ANALYSIS

We used unconditional logistic regression [SAS GENMOD and LOGISTIC procedures (SAS/STAT, 1997)] to model odds ratios (OR) and 95% confidence intervals (CI) as measures of the associations between exposures and chronic renal failure while controlling for potential confounders. Co-variables were considered if they were known or suspected *a priori* to be confounding factors, or if they were associated with both chronic renal failure and each different exposure. The final models were based on the statistical significance of explanatory variables in the model, as assessed by the likelihood-ratio test (Breslow & Day, 1980-1994). To assess the dose-response relations, we performed tests for trend on groups of ordinal variables by assigning each group a score equal to the mean value, fitting the resulting scores into the model (Greenland, 1998), and assessing statistical significance by the likelihood-ratio test. The mean doses of exposures were compared by the Wilcoxon two-sample test (Colton, 1974).

4.4.1 Analysis of analgesic use (Paper I)

In analyses of analgesic use, nonusers of a given analgesic served as the reference category for all comparisons related to that analgesic. The effect-measure of paracetamol use was modified (Rothman, 2002) in the presence of regular aspirin use and a corresponding interaction was seen for aspirin use in the presence of regular paracetamol use. Therefore, we added, in the model, a term for the interaction between paracetamol use and aspirin use, when applicable. In addition, the final model contained terms for sex, age (in 10-year strata), smoking status (lifetime use of <100 or ≥100 cigarettes), level of education (≤9 years, 10 to 12 years, or ≥13 years), and regular use of other analgesics. We examined the associations between analgesic use and disease-specific types of chronic renal failure. Results for both sexes are combined, since associations for men did not differ materially from those for women. To exclude the possibility that analgesic use was prompted by conditions that were precursors to renal failure, we performed analyses in which reported use during the 5 to 10 years before the interview was disregarded. Data on consumption of analgesics were missing for 8 patients (0.9%) and 18 controls (1.8%).

4.4.2 Analysis of socio-economic status (Paper II)

Occupation and educational level were used independently to estimate socio-economic status in analyses of the association between socio-economic status and chronic renal failure. We initially considered height, BMI, number of siblings, cigarette smoking (pack-years), alcohol consumption (grams per week), and cumulative lifetime dose of analgesics during regular use. Smoking and alcohol consumption were grouped in quartiles according to the distribution among control subjects. A simple indicator variable (ever versus never) of regular use was found to sufficiently control for possible confounding by aspirin or paracetamol in relation to socio-economic status. The final analysis model contained terms for age, sex, BMI, cigarette smoking, alcohol consumption, and regular use of aspirin or paracetamol. Analysis of variance was used to investigate the relation between socio-economic status and estimated creatinine clearance (Cockcroft & Gault, 1976).

4.4.3 Analysis of solvent exposure (Paper III)

Odds ratios with 95% CI estimated relative risk of chronic renal failure in different strata of exposure to organic solvents using the risk among non-exposed as reference. The final model contained terms for sex, age, alcohol consumption (grams per week), smoking (cumulative cigarette pack-years), and lifetime cumulative dose of paracetamol and aspirin (grams). Smoking, alcohol, and analgesic doses were categorized according to the distribution among exposed control subjects. We examined the associations of organic solvent exposure with overall chronic renal failure and with disease-specific chronic renal failure such as glomerulonephritis, diabetic nephropathy, and renal vascular disease. To address possible confounding by socio-economic status we analyzed the associations between solvents and chronic renal failure separately for manual and non-manual workers. Adjustment for hypertension was not done, since hypertension may be the result of chronic renal failure rather than its cause and adjustment for this condition in multivariate models will not yield interpretable results. To minimize the possible impact of reverse causation, i.e., that employability and organic solvent exposure were influ-

enced by progressing chronic renal failure; we performed analyses in which exposure during the 10 years before the interview was disregarded. Further, to explore the possibility that recent exposure hastened chronic renal failure progression, exposure prior to the most recent 10 year period was disregarded.

4.4.4 Analysis of occupation and workplace exposures (Paper IV)

Odds ratios with 95% CI estimated relative risks of chronic renal failure overall and of disease-specific types of chronic renal failure in different occupational groups. First, we used the risk among subjects in the largest group (and the group most likely exposed to occupational pollutants), i.e., manufactory workers, as reference. Then, in order to demonstrate the variations in risk more clearly, we rearranged our data to let the occupational groups with the lowest risk (and the least expected exposure to occupational pollutants) serve as reference. In the first analyses, we adjusted for no more than the frequency-matching variables: age and sex. In latter analyses, we added terms for the lifestyle factors: alcohol consumption (grams per week), smoking (cumulative cigarette pack-years), and indicators of regular paracetamol or aspirin use. To investigate if the variation across occupational groups was explained by exposure to occupational pollutants implicated in the literature, we further adjusted for exposure to: exhaust fumes, silica, wood dust, grain dust, textile fibre dust, cellulose dust, lead, mercury, chromium, cadmium, nickel, copper, tin, zinc, and organic solvents.

We examined the associations between occupational exposures and overall chronic renal failure using the risk among non-exposed subjects as reference. Finally, we calculated the hypothetical etiologic fractions (Miettinen, 1974) of all chronic renal failure in the Swedish population that could potentially be attributed to the non-explained excesses observed among manufactory workers, transport/communication/workers, and people involved in administrative/financial/clerical work, respectively. These estimates were based on odds ratios obtained in separate models where people employed in the respective occupational groups were considered to be exposed, while all the others were considered unexposed. Due to significant correlation between occupational group, workplace exposure and our occupational-based measure of socio-economic status, the latter factor was not included in the analyses.

5 RESULTS

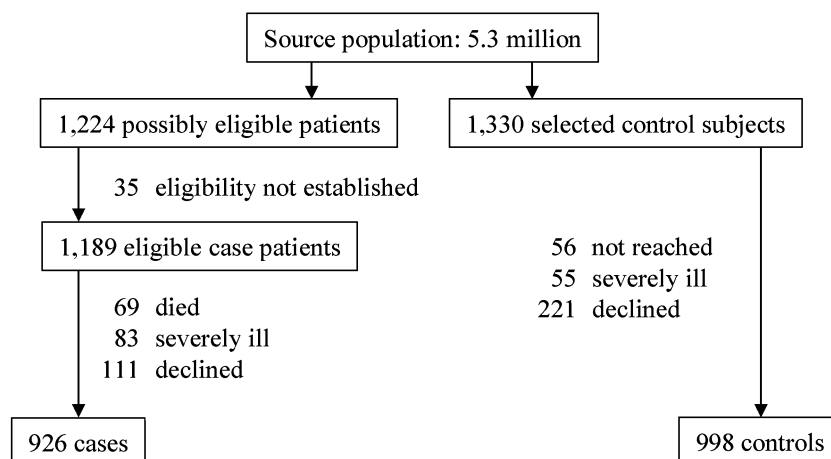


Figure 5. Results from study subject ascertainment.

We identified 1,189 eligible patients and 35 whose eligibility could not be established. Sixty-nine patients died shortly after diagnosis, before they could be contacted, 83 had severe diseases that precluded participation, and 111 patients refused to participate. The remaining 1120 patients were approached, and 926 participated (78% of the 1189 eligible patients). Of 1,330 randomly selected control subjects, 998 (75%) participated, 221 declined, 56 could not be reached, and 55 were too ill to participate (Figure 5). Half of the patients with chronic renal failure were interviewed within one month of inclusion, and 95% were interviewed within 12 months.

Table 2. The distribution of age and sex.

Variable – no. (%)	Cases (n=926)		Controls (n=998)	
	Female sex	329	(35.5)	345
Age at interview (years)				
18-24	11	(1.2)	20	(2.0)
25-34	63	(6.8)	58	(5.8)
35-44	95	(10.3)	97	(9.7)
45-54	193	(20.8)	186	(18.6)
55-64	186	(20.1)	204	(20.4)
65-74	378	(40.8)	433	(43.4)

There were almost twice as many men (n=1,250) as women (n=674). As expected from the frequency-matched design, the mean age was identical among case patients and control subjects, and it was similar among men (58 years) and women (57 years) (Table 2).

Table 3. Diagnoses among case patients.

Diagnosis	n	(%)*	n	(%)†
Diabetic nephropathy	286	(30.9)		
Glomerulonephritis	222	(24.0)		
IgA nephritis			63	(28.4)
No renal biopsy/unclassified			54	(24.3)
Unclassified			42	(18.9)
Proliferative			26	(11.7)
Focal & segmental sclerosis			16	(7.2)
Crescentic glomerulonephritis			12	(5.4)
Other			9	(4.1)
Renal vascular disease	139	(15.0)		
Benign hypertension			125	(89.9)
Malignant hypertension			8	(5.8)
Other			6	(4.3)
Hereditary disease	98	(10.6)		
Polycystic kidney disease			83	(84.7)
Other			10	(10.2)
Agenesis or dysgenesis			5	(5.1)
Systemic disease/Vasculitis	82	(8.9)		
Amyloidosis			20	(24.4)
Wegener's granulomatosis			12	(14.6)
Rheumatoid arthritis			11	(13.4)
Multiple myeloma			11	(13.4)
Systemic lupus erythematosus			9	(11.0)
Haemolytic-uraemic syndrome			8	(9.8)
Other vasculitis			6	(7.3)
Other systemic disease			5	(6.1)
Other renal disease	99	(10.7)		
Unknown renal disease			44	(44.4)
Interstitial nephritis			27	(27.3)
Chronic Pyelonephritis			21	(21.2)
Other			6	(6.1)
Phenacetin nephropathy			1	(1.0)

* Percent of all cases

† Percent of total within diagnosis group

The distribution of patients with chronic renal failure according to underlying disease is shown in Table 3. Diagnoses were based on renal biopsies in 30% of the patients (n=277). Diabetic nephropathy was the most common underlying renal disease diagnosis (31%), whereas nearly a fourth of the patients had glomerulonephritis (24%). In 61% (n=135) of the patients with glomerulonephritis a renal biopsy was performed. Merely one patient was classified as having phenacetin (analgesic) nephropathy and 3% had interstitial nephritis.

Of the 926 patients in this study, 120 (13%) reported not being diagnosed with a renal disease before inclusion. Forty-two percent (n=50) of these patients had diabetic nephropathy, while 20% (n=24) and 15% (n=18) had renal vascular disease and glomerulonephritis, respectively. The mean disease duration reported by the 798 patients previously diagnosed with renal disease was 10 years (median, 4 years; interquartile range, 2-13 years). Information on disease diagnosis was missing for 8 patients.

A majority of the chronic renal failure patients were in the pre-uraemic stage, and so not in need of renal replacement therapy. The median value of the predicted creatinine clearance [Cockcroft-Gault formula (Cockcroft & Gault, 1976)] at time of entry into the study was 21 ml/min (range, 2 to 53 ml/min) (Table 4). Six percent (n=57) of the patients had a creatinine clearance <10 ml/min while the clearance was \geq 17 ml/min among 75% of the patients. No statistically significant differences in renal function (clearance) between patients in the different socio-economic status groups were found (P=0.07).

Table 4. Measures of renal function among patients with chronic renal failure.

	Median	Range
Serum creatinine (μ mol/l)* at inclusion		
Men	336	300-2,475
Women	281	250-1,680
Creatinine clearance (ml/min) [†]		
Men	22	2-53
Women	19	3-35

* Conversion factor for conventional Unit (mg/dl) is 88.4.

[†] Predicted creatinine clearance (Cockcroft-Gault formula).

Conversion factor for SI Unit (ml/s) is 0.0167.

The distributions of other risk factors than the investigated that possibly act as confounders are shown in Table 5. More case patients reported smoking for more than 6 months. In addition, more cases were found among the heaviest cigarette smokers (Table 5). Control subjects that reported smoking, more often reported regular paracetamol use than non-smokers (15% vs. 8%). The corresponding proportions for regular aspirin use were 23% and 15%. The largest proportions of subjects (~18%) classified in the heaviest smoking category (>27.5 pack-years) were found among unskilled and skilled manual workers. Sixty-two percent and 52% of the solvent exposed and unexposed control subjects, respectively, were classified as smokers. Smoking was most common among transport and communication workers and manufacturing workers (67%), while only 43% of the control subjects in the agricultural, forestry, and fishing industry work grouped reported smoking for more than 6 months.

Control subjects tended to use more alcohol but the proportion of subjects consuming more than 66 grams of alcohol per week (~75 centilitres of wine) was larger among the case patients (Table 5). Eleven percent and 17% of the alcohol consumers and non-

consumers, respectively, reported regular paracetamol use, whereas no difference in regular use of aspirin was seen (19% in both groups). The largest proportion of reported alcohol abstinence was found among the unskilled manual workers (30%) and self-employed subjects (32%), while weekly alcohol consumption within the highest quartile was most common among the skilled manual subjects (23%), and the professionals (25%). Twenty-one and 18% of the solvent exposed and unexposed control subjects, respectively, reported alcohol abstinence. Alcohol abstinence was most common among (i) agricultural, forestry, and fishing industry workers (29%) and (ii) service occupations employees (27%), while subjects grouped among (iii) the technical, scientific, humanistic, and artistic workers (89%) and (iv) the administrative, financial, and clerical workers (88%) reported most alcohol consumption.

Table 5. Other risk factors for chronic renal failure.

Variable – no. (%)	Cases		Controls	
	(n=926)		(n=998)	
Alcohol intake (grams/week)				
None	234	(25.3)	202	(20.2)
Up to 17.6	217	(23.4)	258	(25.8)
17.7 to 33	116	(12.5)	135	(13.5)
33.1 to 66	143	(15.4)	190	(19.0)
More than 66	206	(22.2)	209	(20.9)
Missing information	10	(1.1)	4	(0.4)
Cigarette smoking				
< 6 months smoking	371	(40.1)	440	(44.1)
1 - 6.6 pack years	78	(8.4)	137	(13.7)
6.7 - 16 pack years	147	(15.9)	140	(14.0)
16.1 - 27.5 pack years	156	(16.9)	141	(14.1)
> 27.5 pack years	161	(17.4)	130	(13.0)
Missing information	13	(1.4)	10	(1.0)
Body mass index*				
≤ 25	458	(49.5)	465	(46.6)
> 25	442	(47.7)	508	(50.9)
Missing information	26	(2.8)	25	(2.5)
Reported diabetes diagnosis	329	(35.5)	68	(6.8)
Reported hypertension diagnosis	706	(76.2)	164	(16.4)
Missing information	3	(0.3)	5	(0.5)

* The weight in kilograms divided by the square of the height in meters.

The patients tended to have a lower BMI than the control subjects and more than 50% of the subjects in the socio-economic status groups: (i) skilled manual workers, (ii) assistant non-manual employees, or (iii) self-employed, had a BMI above 25. The proportions of subjects that reported being diagnosed with diabetes or hypertension were much larger among the case patients than among controls (Table 5). The variation was small in the proportions of reported hypertension or diabetes diagnoses between socio-economic status groups.

5.1 RESULTS FOR CHRONIC RENAL FAILURE OVERALL

5.1.1 Analgesics use (Paper I)

Lifetime consumption of analgesics is shown in Table 6. Analgesic use was more common among the case patients. Overall, 86% of the patients and 75% of the control subjects reported the use of any non-narcotic analgesic.

Table 6. Lifetime consumption of analgesics.*

	Case patients (n=918)		Control subjects (n=980)	
Paracetamol use– no. (%)				
Subjects without regular aspirin use				
Never used	230	(24.8)	376	(37.7)
Ever used	345	(37.3)	413	(41.4)
Use or used regularly	105	(11.3)	71	(7.1)
Subjects with any regular aspirin use				
Never used	101	(10.9)	83	(8.3)
Ever used	242	(26.1)	108	(10.8)
Use or used regularly	130	(14.0)	50	(5.0)
Aspirin use– no. (%)				
Subjects without regular paracetamol use				
Never used	224	(24.2)	363	(36.4)
Ever used	459	(49.6)	496	(49.7)
Use or used regularly	213	(23.0)	141	(14.1)
Subjects with any regular paracetamol use				
Never used	59	(6.4)	35	(3.5)
Ever used	176	(19.0)	86	(8.6)
Use or used regularly	130	(14.0)	50	(5.0)
Dextropropoxyphene – no. (%)				
Never used	695	(75.1)	812	(81.4)
Ever used	223	(24.1)	168	(16.8)
Use or used regularly	122	(13.2)	64	(6.4)
Non-aspirin NSAIDs – no. (%)				
Never used	724	(78.2)	793	(79.5)
Ever used	194	(21.0)	187	(18.7)
Use or used regularly	106	(11.5)	77	(7.7)
Codeine – no. (%)				
Never used	730	(78.8)	844	(84.6)
Ever used	188	(20.3)	136	(13.6)
Use or used regularly	66	(7.1)	37	(3.7)
Pyrazolones – no. (%)				
Never used	827	(89.3)	916	(91.8)
Ever used	91	(9.9)	64	(6.4)
Use or used regularly	46	(5.0)	23	(2.3)
Phenacetin – no. (%)				
Never used	901	(97.3)	963	(96.5)
Ever used	17	(1.8)	17	(1.7)
Use or used regularly	4	(0.4)	6	(0.6)

* Data on consumption of analgesics were missing for 8 case patients and 18 controls.

Fifty-one percent of the patients and 29% of the controls had used at least one analgesic regularly. Aspirin and paracetamol were used regularly by 37% and 25%, respectively, of the case patients and by 19% and 12 percent, respectively, of the controls. A total of 22% of male patients and 10% of male controls reported regular paracetamol use, and 38% of male patients and 20% of male controls reported regular aspirin use. Thirty-two percent of female patients and 16% of female controls reported regular paracetamol use, and 36% of female patients and 17% of female controls reported regular aspirin use. Regular use of analgesics with paracetamol or aspirin was most common among control subjects in the unskilled manual worker group (30%), and least common among the professionals (20%) (data not shown). More patients than control subjects used other non-narcotic analgesics as well as aspirin and paracetamol (Table 6).

Due to the interaction between paracetamol use and aspirin use regarding the association with chronic renal failure development, the effects of paracetamol use and aspirin use are presented in the absence and the presence of regular use of aspirin and paracetamol, respectively.

Paracetamol use in the absence of regular aspirin use

Among subjects not reporting regular aspirin use, the regular use of paracetamol was associated with a risk of chronic renal failure that was 2.5 times as high as that for non-users of paracetamol. The risk increased with an increasing cumulative lifetime dose ($P_{\text{trend}} < 0.001$) (Table 7). The average dose used during periods of regular paracetamol use also correlated with risk ($P_{\text{trend}} < 0.001$) so that those who took 500 g or more per year (≥ 1.4 g/day) during periods of regular use had an odds ratio for chronic renal failure of 5.3 (95% CI, 1.8-15.1). The duration of use was unrelated to risk (data not shown).

Aspirin use in the absence of regular paracetamol use

Among subjects who did not use paracetamol regularly, the regular use of aspirin was associated with a risk of chronic renal failure that was 2.5 times as high as that for non-users of aspirin (Table 7). This risk increased significantly with an increasing cumulative lifetime dose of aspirin ($P_{\text{trend}} = 0.01$) and with an increasing average dose during periods of regular use ($P_{\text{trend}} = 0.004$), but not with an increasing duration of use. Among those with an average intake of 500 g or more of aspirin per year during periods of regular use, the odds ratio for chronic renal failure was 3.3 (95% CI, 1.4-8.0).

Paracetamol use in addition to aspirin use

The odds ratio for chronic renal failure among subjects reporting regular use of both paracetamol and aspirin was 2.2 (95% CI, 1.4-3.5). The reference group in this estimation of the relative risk was subjects reporting regular aspirin use. The trend toward greater risk with an increasing cumulative lifetime dose of paracetamol was statistically significant ($P = 0.03$), with a risk that was 2.4 times as high (95% CI, 1.4-4.4) for subjects who had consumed a total of more than 500 g of paracetamol than for those who had used aspirin only.

Aspirin use in addition to paracetamol use

The odds ratio for chronic renal failure was 1.6 (95% CI, 0.9-2.7) among regular users of both aspirin and paracetamol as compared with regular users of paracetamol only. The trend toward greater risk with increasing cumulative lifetime dose of aspirin was significant (P=0.02).

Use of other analgesics

After adjustment for paracetamol use and aspirin use, no associations between the use of the other drugs presented in Table 6 and the risk of chronic renal failure remained. The adjusted odds ratios associated with the regular use of dextropropoxyphene, non-aspirin NSAIDs, codeine, and pyrazolones were 1.0, 1.0, 0.9, and 1.3, respectively.

Table 7. Odds ratios for chronic renal failure associated with lifetime use of either paracetamol or aspirin among subjects who did not use the other analgesic regularly.*

	Paracetamol use		Aspirin use	
	OR	(95% CI)	OR	(95% CI)
Never used	1.0		1.0	
Ever used	1.3	(1.0-1.6)	1.5	(1.2-1.8)
Use or used regularly	2.5	(1.7-3.6)	2.5	(1.9-3.3)
Cumulative dose				
1-99 g	1.2	(0.9-1.5)	1.4	(1.1-1.7)
100-499 g	1.3	(0.9-1.8)	1.6	(1.2-2.1)
≥500 g	3.3	(2.0-5.5)	1.9	(1.3-2.9)

* Adjustments are made for age, sex, level of education, smoking status, use or non-use of other analgesics, and the interaction between aspirin use and paracetamol use. P<0.001 and P=0.01 for the trend toward greater risk with increasing cumulative doses of paracetamol and aspirin, respectively. Regular use was defined as the use of at least two tablets per week for a period of two months or longer.

5.1.2 Socio-economic status (Paper II)

The risk of chronic renal failure was inversely related to socio-economic status inferred from occupations of the individual study participants (Table 8). The relationship with household socio-economic status was even clearer. The gradients among women were at least as marked as those among men. Compared with women in families with the highest socio-economic status, female members of families with only unskilled workers had a 110% (OR, 2.1; 95% CI 1.1-4.0) excess risk for chronic renal failure following adjustments for potential confounding factors. The corresponding excess among men was 60% (OR, 1.6; 95% CI, 1.0-2.6). Subjects with 9 years of schooling had a 30% (OR, 1.3; 95% CI, 1.0-1.7) higher risk compared with those who went to university, but this excess was mainly confined to men.

Table 8. The risk of chronic renal failure in relation to socio-economic status (SES).

Variable	Men				Women				Both sexes	
	Cases	Controls		Cases	Controls					
	N	n	OR* 95% CI†	n	n	OR* 95% CI†	OR* 95% CI†	OR* 95% CI†		
Household SES‡										
professionals	100	147	1.0 ref	38	63	1.0 ref	1.0 Ref			
intermediate non-manual	120	135	1.2 (0.8-1.7)	51	80	0.9 (0.5-1.6)	1.1 (0.8-1.4)			
assistant non-manual	97	103	1.3 (0.9-2.0)	86	72	1.5 (0.9-2.7)	1.4 (1.0-1.9)			
Skilled manual	170	153	1.5 (1.0-2.1)	62	53	1.5 (0.8-2.7)	1.5 (1.1-2.0)			
unskilled manual	65	59	1.6 (1.0-2.6)	71	44	2.1 (1.1-4.0)	1.9 (1.3-2.7)			
self-employed	39	55	1.1 (0.6-1.8)	19	33	0.7 (0.3-1.5)	0.9 (0.6-1.4)			
Individual SES§										
professionals	86	128	1.0 ref	22	34	1.0 ref	1.0 Ref			
intermediate non-manual	95	117	1.1 (0.8-1.7)	40	73	0.9 (0.4-1.8)	1.0 (0.7-1.4)			
assistant non-manual	72	72	1.5 (0.9-2.3)	90	81	1.6 (0.8-3.1)	1.5 (1.1-2.2)			
Skilled manual	227	194	1.6 (1.1-2.3)	43	51	1.1 (0.5-2.3)	1.5 (1.1-2.0)			
unskilled manual	73	75	1.4 (0.9-2.3)	111	81	1.9 (0.9-3.8)	1.7 (1.2-2.5)			
self-employed	30	48	1.0 (0.6-1.8)	6	11	0.7 (0.2-2.3)	1.0 (0.6-1.6)			
Years of education										
≥ 13 years	109	142	1.0 ref	59	78	1.0 ref	1.0 Ref			
10-12 years	129	150	1.2 (0.8-1.7)	80	96	0.9 (0.6-1.5)	1.1 (0.8-1.4)			
≤ 9 years	350	355	1.4 (1.0-1.9)	187	170	1.1 (0.7-1.9)	1.3 (1.0-1.7)			

* Odds ratios adjusted for age, sex, body mass index, cigarette smoking, alcohol intake, and regular aspirin and/or paracetamol use.

† Ninety-five percent confidence interval.

‡ The highest occupational socio-economic group within the subjects' family.

§ The highest individual occupational socio-economic group

5.1.3 Organic solvent exposure (Paper III)

The industry where most solvent exposure occurred was manufacturing. Seventy percent of the case patients and 62% of the control subjects who had reported solvent exposure were exposed during manufacturing work (Table 9). The largest group was metal workers (24% of all solvent exposed patients and 21% of all exposed controls), while 6% of the exposed case patients and 7% of the exposed control subjects were painters and floor layers. The crude relative risk estimates in each of the occupational groups, calculated from the exposure frequencies in Table 9, all were insignificant and close to 1. The Mantel-Haenszel estimate (Schlesselman & Stolley, 1982) of relative chronic renal failure risk, pooled across occupational group strata was 0.95 (95% CI, 0.76-1.19).

Exposure to organic solvents was not associated with an increased risk of chronic renal failure after adjustment for potential confounders (OR, 1.1; 95% CI, 0.81-1.25). Nor was there any evidence of a dose-response trend with increasing lifetime cumulative solvent exposure (Table 10). Furthermore, neither duration (years) nor exposure frequency (days per month) showed any dose-dependent relationships with risk of chronic renal failure (data not shown).

Table 9. Distribution of solvent exposed and unexposed subjects by occupational group.*

Occupational group – no. (%)	Case patients		Control subjects	
	Exposed (n=276)	Unexposed (n=637)	Exposed (n=288)	Unexposed (n=703)
Technical, scientific, humanistic, and artistic work	15 (5.4)	76 (11.9)	35 (12.1)	113 (16.1)
Health care and social work	6 (2.2)	68 (10.7)	10 (3.5)	96 (13.7)
Administrative, financial, and clerical work	6 (2.2)	127 (19.9)	5 (1.7)	119 (16.9)
Commercial work	6 (2.2)	70 (11.0)	9 (3.1)	83 (11.8)
Agricultural, forestry, and fishing industry work	11 (4.0)	34 (5.3)	20 (6.9)	47 (6.7)
Transport and communications work	15 (5.4)	54 (8.5)	11 (3.8)	42 (6.0)
Manufacturing work	193 (69.9)	137 (21.5)	180 (62.5)	127 (18.1)
Service occupations	24 (8.7)	53 (8.3)	18 (6.2)	57 (8.1)
Unclassified†	0 -	18 (2.8)	0 -	19 (2.7)

* Main occupation during exposure among exposed subjects and main occupation in the lifetime occupational history among subjects unexposed to organic solvents.

† Unexposed subjects reporting a total employment period of less than 1 year.

Table 10. Adjusted odds ratios (OR) and 95% confidence intervals (95% CI) for chronic renal failure associated with highest solvent exposure intensity level and lifetime cumulative solvent exposure dose.*

	Case patients (n=913)	Control subjects (n=991)	OR†	(95% CI)
Unexposed	637	703	1	(referent)
Ever exposed	276	288	1.01	(0.81-1.25)
Solvent exposure level‡				
Low	96	103	1.07	(0.78-1.46)
Intermediate	72	92	0.86	(0.61-1.22)
High	108	93	1.08	(0.78-1.49)
Lifetime cumulative dose§				
1 st quartile	69	72	1.10	(0.76-1.59)
2 nd quartile	58	72	0.88	(0.60-1.29)
3 rd quartile	72	73	0.91	(0.63-1.32)
4 th quartile	77	71	1.15	(0.79-1.65)

* Exposure levels; (a) *Unexposed*, < 3%; (b) *Low*, ≥ 3 and < 10%; (c) *Intermediate*, ≥ 10 and < 30%; (d) *High*, ≥ 30%, Hygienic Effect (HE, the sum of fractional contributions from different organic solvents in relation to their respective occupational exposure limit value in 1996), respectively.

† Odds ratios adjusted for age, sex, alcohol consumption, cigarette smoking, and consumption of paracetamol and aspirin.

‡ Estimated mean exposure (HE) in each class; (a) *Low*, 0.067, (b) *Intermediate*, 0.22, (c) *High*, 1, respectively.

§ The product of the exposure intensity level (HE), exposure frequency (days per month) and duration (years) of the solvent exposure, summed over all work periods in the subjects' occupational history.

The negative results pertained to both men and women. Among male patients and control subjects, 41% (n=242) and 38% (n=245), respectively, reported organic solvent exposure, while the corresponding proportions among females were only 10% (n=34) and 13% (n=43). Since only 14% of the solvent exposed subjects were women, the precision of female-specific data was limited. Stratified analyses confined to the socio-economic classes “manual workers” and “non-manual workers” also showed the same absence of association between solvent exposure and risk of chronic renal failure (data not shown).

5.1.4 Occupation and workplace exposures (Paper IV)

The proportion of subjects reporting at least one employment period with a duration of one year or more was similar among cases (96%; n=893) and controls (97%; n=966). Further, the case patients and control subjects were similar with regard to number of reported employment periods (mean, 3.6; median, 3, in both groups), and in the number of reported occupations (cases mean, 2.1; controls mean, 2.0; median, 2, in both groups). The main occupation was most commonly within the manufacturing work group, both among case patients (31%; n=281) and control subjects (27%; n=263). Compared with subjects in the manufacturing work group, subjects with (i) technical, scientific, humanistic, or artistic work occupations, (ii) health care and social work occupations, and (iii) agricultural, forestry, or fishing industry work occupations, all had similar low risk of chronic renal failure (Table 11). The Pearson chi-squared test (7 degrees of freedom) applied to the frequencies in Table 11 gives P=0.001, demonstrating significant heterogeneity between the occupational groups.

Table 11. Odds ratios (OR) for chronic renal failure associated with main occupation.*

	Cases	Controls	OR [†]	(95% CI)
Manufacturing work	281	263	1	reference
Administrative, financial, and clerical work	145	132	0.96	(0.71-1.30)
Technical, scientific, humanistic, and artistic work	99	154	0.58	(0.43-0.79)
Health care and social work	80	113	0.59	(0.41-0.85)
Commercial work	89	100	0.81	(0.57-1.13)
Service occupations	78	77	0.90	(0.62-1.30)
Transport and communications work	73	55	1.22	(0.83-1.81)
Agricultural, forestry, and fishing industry work	48	72	0.63	(0.42-0.95)

* Reported main occupation among case patients (n=893) and control subjects (n=966) with at least one year of employment.

† Odds ratios and 95% confidence intervals (95% CI) adjusted for the frequency-matching variables age and sex.

The most common occupational exposure was exhaust fumes (including CO and NO₂) of which 30% of the case patients and 27% of the control subjects reported any exposure. The proportions of subjects ever exposed to silica dust were 11% and 8.1% among case patients and control subjects, respectively. Exposure to wood dust (cases; 6.8%, controls; 6.7%), and grain dust (cases; 6.5%, controls; 7.3%) was relatively rare, but they were the most frequent exposures reported among the organic dusts. Exposure to textile fibre dust

(cases; 2.2%, controls; 2.1%), and cellulose dust (cases; 1.4%, controls; 0.9%) occurred more seldom. Among the metals investigated, lead exposure was most frequent, being reported by 9.1% of the case patients, and 9.6% of the control subjects. Exposure to mercury (cases; 3.3%, controls; 3.9%), chromium (cases; 2.1%, controls; 2.3%), cadmium (cases; 1.1%, controls; 0.8%), and nickel (cases; 0.8%, controls; 1.1%) was rare, as was exposure to copper, tin, and zinc.

Neither of the organic dust agents were associated with an increased risk of chronic renal failure after adjustments for potential confounders (wood dust; OR, 0.95, grain dust; OR, 0.94, textile fibre dust; OR, 0.93) (Table 12). Similarly, no risk elevations were seen among subjects exposed to the heavy metals; lead, mercury, and chromium relative to non-exposed (OR, 0.97; 0.86; and 0.87, respectively).

The odds ratio for exposure to exhaust fumes was also close to unity (OR, 1.18), and no dose-risk trend was observed (Table 12). Exposure to cadmium was associated with a slightly increased risk of chronic renal failure. The confidence interval, however, included 1 (OR, 1.26; 95% CI, 0.48-3.43). Our results were suggestive of an increasing risk with increasing cumulative cadmium exposure, but the precision was poor due to few highly exposed subjects. Subjects with exposure to silica dust above 1/30 of the OEL had a 40% (OR, 1.39; 95% CI, 1.00-1.94) higher risk of chronic renal failure compared with subjects with exposure below this level or with no reported exposure. Our data also suggested a dose-risk trend, albeit statistically non-significant ($P_{\text{trend}} = 0.086$).

The results already presented in Table 11 imply that the combined exposure to risk factors for chronic renal failure associated with specific occupational groups is similar and least among subjects in the: (i) technical, scientific, humanistic, or artistic work, (ii) health care and social work, and (iii) agricultural, forestry, or fishing industry work occupational groups. In comparison with subjects in these three groups, workers within service occupations had a 51% higher risk of chronic renal failure, manufactory workers had a 68% higher risk, while workers within transport and communications had a doubled risk (Table 13). These differences in risk decreased (OR, 1.35, 1.53, and 1.91, respectively) following adjustments for the lifestyle related factors: cigarette smoking, alcohol consumption, and regular use of paracetamol or aspirin. Further adjustments for the occupational exposure agents investigated in this thesis attenuated the relative risk estimates by no more than 0.7%, 4%, and 5%, respectively. The variation between subjects with the lowest and the highest chronic renal failure risk remained significantly 1.5-fold and 1.8-fold (Table 13).

Contrary to workers within manufacturing, transport and service industries, the relative risk estimates for subjects in the commercial, and administrative / financial / clerical categories increased following adjustments for the lifestyle related factors, and in these two occupational groups, further adjustments for exposure the occupational pollutants did not change the observed odds ratios. The adjusted differences in chronic renal failure risk, compared with the three low-risk groups, were 42% and 65% among commercial and administrative / financial / clerical workers, respectively (Table 13).

Table 12. Odds ratios and 95% confidence intervals (CI) for Chronic Renal Failure of the most prevalent occupational exposures.

Exposure		Cases (n=913)	Controls (n=991)	OR*	95% CI
Exhaust fumes [†]	Unexposed	637	725	1	reference
	Exposed	276	266	1.18	(0.94-1.48)
	- low	100	88	1.28	(0.92-1.78)
	- medium	97	88	1.30	(0.93-1.82)
	- high	79	90	0.96	(0.67-1.37)
Silica dust [‡]	Unexposed	811	911	1	reference
	Exposed	102	80	1.39	(1.00-1.94)
	- low	25	27	1.05	(0.58-1.90)
	- medium	39	26	1.63	(0.96-2.79)
	- high	38	27	1.48	(0.88-2.54)
Wood dust	Unexposed	851	925	1	reference
	Exposed	62	66	0.95	(0.65-1.39)
	- low	19	22	0.82	(0.42-1.57)
	- medium	23	21	1.09	(0.58-2.07)
	- high	20	23	0.95	(0.50-1.81)
Grain dust	Unexposed	854	919	1	reference
	Exposed	59	72	0.94	(0.64-1.37)
	- low	19	24	0.95	(0.49-1.83)
	- medium	17	24	0.69	(0.35-1.35)
	- high	23	24	1.20	(0.65-2.22)
Textile dust	Unexposed	893	970	1	reference
	Exposed	20	21	0.93	(0.48-1.79)
	- low	11	7	1.39	(0.51-3.98)
	- medium	4	7	0.61	(0.15-2.12)
	- high	5	7	0.75	(0.21-2.49)
Lead	Unexposed	830	896	1	reference
	Exposed	83	95	0.97	(0.70-1.36)
	- low	24	32	0.81	(0.45-1.43)
	- medium	31	31	1.14	(0.67-1.95)
	- high	28	32	0.98	(0.56-1.68)
Mercury	Unexposed	883	952	1	reference
	Exposed	30	39	0.86	(0.51-1.43)
	- low	9	13	0.88	(0.35-2.12)
	- medium	13	13	1.03	(0.45-2.38)
	- high	8	13	0.67	(0.25-1.67)
Chromium	Unexposed	894	968	1	reference
	Exposed	19	23	0.87	(0.45-1.67)
	- low	7	8	0.75	(0.25-2.22)
	- medium	3	8	0.40	(0.08-1.52)
	- high	9	7	1.58	(0.57-4.56)
Cadmium	Unexposed	903	983	1	reference
	Exposed	10	8	1.26	(0.48-3.43)
	- low	2	3	0.80	(0.10-5.07)
	- medium	3	3	0.98	(0.17-5.78)
	- high	5	2	2.23	(0.46-15.98)

* Odds ratios adjusted for sex, age, cigarette smoking, alcohol consumption, and regular paracetamol and/or aspirin use. *High* is total exposure in the upper tertile, *medium* in the middle tertile, and *low* is exposure in the lowest tertile.

[†] Carbomonoxide and Nitrogen dioxide in combustion exhaust fumes.

[‡] Silica in sand, cement, coal, or rocks.

Table 13. Odds ratios for chronic renal failure associated with main occupation. Subjects in three low-risk groups* served as reference.

	OR [†]	(95% CI)	OR [‡]	(95% CI)	OR [§]	(95% CI)
Service occupations	1.51	(1.05-2.16)	1.35	(0.92-1.98)	1.34	(0.91-1.97)
Manufacturing work	1.68	(1.31-2.15)	1.53	(1.18-1.98)	1.47	(1.11-1.94)
Transport and communications work	2.05	(1.39-3.04)	1.91	(1.27-2.88)	1.82	(1.19-2.77)
Commercial work	1.35	(0.97-1.89)	1.42	(1.00-2.01)	1.42	(1.00-2.03)
Administrative, financial, and clerical work	1.61	(1.20-2.15)	1.65	(1.21-2.24)	1.65	(1.21-2.26)

* Subjects with their main occupation falling in the (1) Technical, scientific, humanistic, and artistic, (2) Health care and social, and (3) Agricultural, forestry, and fishing industry work categories (227 cases; 339 controls) constituted the reference group.

[†] Odds Ratios (OR) and 95% confidence intervals (95% CI) adjusted for age and sex.

[‡] OR and 95% CI adjusted for age, sex, cigarette smoking, alcohol consumption, and regular use of paracetamol and/or aspirin.

[§] OR and 95% CI adjusted for age, sex, smoking, alcohol consumption, regular use of paracetamol and/or aspirin, and occupational exposure to exhaust fumes, silica, wood dust, grain dust, textile fibre dust, cellulose dust, lead, mercury, chromium, cadmium, nickel, copper, tin, zinc, and organic solvents.

In order to estimate potential etiologic fractions (Miettinen, 1974) attributed to the unexplained excesses among some high-risk occupational groups, we modelled, in separate models, the relative risk associated with employment in the occupational group, using all the other subjects (unexposed to that particular occupational group) as reference. Adjustments were made for the same covariates as in the fully adjusted models described above. The OR and etiologic fraction for manufactory work were 1.14 (95% CI, 0.90-1.46) and 3.9%, respectively. For transport and communications work, the corresponding figures were 1.39 (95% CI, 0.94-2.05) and 2.3%, and for administrative/financial/clerical work they were 1.33 (95% CI, 1.00-1.76) and 4.0%.

5.2 RESULTS BY UNDERLYING RENAL DISEASE

To elucidate possible differences in chronic renal failure risk associated with the investigated exposures between patients with different renal diseases underlying chronic renal failure, we compared patients within subtypes of chronic renal failure with all control subjects.

5.2.1 Analgesics use (Paper I)

The odds ratios associated with regular paracetamol use in the absence of regular aspirin use were greater than 1.0 for all types of renal failure (Table 14), but they were significant only for renal failure classified as diabetic nephropathy and that associated with systematic disease or vasculitis. Dose-related trends in risk were significant for all diagnoses except glomerulonephritis and renal vascular disease. In analyses of aspirin use in the absence of regular paracetamol use, the strongest association was found between aspirin use and chronic renal failure associated with “other renal disease,” but the odds ratio was greater than 2.0 for all types of chronic renal failure except that linked to

systemic disease or vasculitis (Table 14). The dose-related trends in risk, however, were non-significant for all types except glomerulonephritis (P=0.008).

The types of chronic renal failure most strongly associated with regular use of paracetamol in addition to regular aspirin use were renal failure linked to diabetes (OR, 2.8; 95% CI, 1.5-5.4) and renal failure linked to systemic disease or vasculitis (OR, 5.1; 95% CI, 1.5-17.6), but estimates of relative risks of approximately 2.0 were found for all types of chronic renal failure (data not shown). A similar pattern of associations was found between aspirin use and specific types of chronic renal failure among regular users of paracetamol, but there were lower point estimates for the risk associated with diabetic nephropathy (OR, 1.7; 95% CI, 0.8-3.4) and that associated with chronic renal failure classified as “other renal disease” (OR, 1.4; 95% CI, 0.5-3.7).

Table 14. Odds ratios for chronic renal failure associated with isolated regular use of paracetamol or aspirin according to the type of underlying renal disease.*

	Paracetamol use		Aspirin use	
	n	OR [†] (95% CI)	n	OR [‡] (95% CI)
Diabetic nephropathy	42	3.6 (2.1-6.0)	68	2.9 (1.9-4.5)
Glomerulonephritis	17	1.6 (0.9-3.0)	57	2.6 (1.4-4.8)
Renal vascular disease	12	1.7 (0.8-3.7)	39	2.1 (1.3-3.5)
Hereditary renal disease	6	2.2 (0.8-5.9)	19	3.1 (1.6-6.0)
Systemic disease or vasculitis	15	2.8 (1.2-6.5)	8	1.1 (0.4-2.8)
Other renal disease	13	2.1 (0.9-4.6)	22	3.7 (1.8-7.7)

* Adjustments were made for age, sex, level of education, smoking status, use of other analgesics, and the interaction between aspirin use and paracetamol use. Regular use was defined as the use of at least two tablets per week for a period of two months or longer.

[†] The reference group was nonusers of paracetamol without regular aspirin use.

[‡] The reference group was nonusers of aspirin without regular paracetamol use.

To separate the effects of drugs from the effects of the underlying disease, we analyzed the association between analgesic use and the risk of chronic renal failure among 67 control subjects and 324 patients with diabetes (both insulin dependent and non-dependent). The odds ratios were 4.0 (95% CI, 1.0-16.1) and 1.4 (95% CI, 0.7-3.1) associated with regular paracetamol use and regular aspirin use, respectively, in the absence of the other analgesic.

5.2.2 Socio-economic status (Paper II)

Household socio-economic status was associated with a more than 2-fold risk gradient for all major types of chronic renal failure, although the dose-response curve varied slightly in appearance between diagnostic categories. The relationship appeared less convincing for the miscellaneous group of underlying pathology. The trend with individual level of education was weaker for chronic renal failure classified as glomerulonephritis than for the other major types, and it was absent for the miscellaneous group (Table 15).

Table 15. The risk of type-specific chronic renal failure in relation to socio-economic status.

Variable	Diabetic nephropathy (n=286)		Glomerulo-nephritis (n=222)		Renal vascular disease (n=139)		Other* (n=279)	
	Adjusted odds ratios and 95% confidence intervals†							
Household SES‡								
professionals	1.0	ref	1.0	ref	1.0	ref	1.0	Ref
intermediate non-manual	0.8	(0.5-1.4)	1.0	(0.6-1.6)	2.2	(1.1-4.5)	1.1	(0.7-1.7)
assistant non-manual	1.5	(0.9-2.5)	1.4	(0.8-2.3)	2.5	(1.2-5.2)	1.2	(0.8-2.0)
skilled manual	1.8	(1.1-2.8)	1.3	(0.8-2.1)	2.4	(1.1-4.8)	1.2	(0.8-1.9)
unskilled manual	2.4	(1.4-4.2)	2.2	(1.3-3.8)	2.5	(1.1-5.7)	1.4	(0.8-2.4)
self-employed	0.9	(0.5-1.9)	1.0	(0.5-2.1)	2.0	(0.8-4.9)	0.8	(0.4-1.6)
Years of education								
≥ 13 years	1.0	ref	1.0	ref	1.0	ref	1.0	Ref
10-12 years	1.5	(0.9-2.4)	1.4	(0.9-2.2)	1.6	(0.7-3.4)	0.7	(0.5-1.1)
≤ 9 years	2.0	(1.2-3.2)	1.4	(0.9-2.3)	2.4	(1.2-4.7)	0.8	(0.5-1.2)

* Hereditary renal disease, systemic disease/vasculitis, and other renal disease.

† Adjustments made for age, sex, body mass index, cigarette smoking, alcohol intake, and regular aspirin and/or paracetamol use.

‡ The highest occupational socio-economic status (SES) group within the subjects' family.

Table 16. Adjusted odds ratios and 95% confidence intervals for various classes of chronic renal failure (CRF) associated with lifetime cumulative solvent exposure dose.*

	Glomerulo-nephritis (n=217)		Diabetic Nephropathy (n=282)		Renal vascular disease (n=138)		Other renal CRF (n=276)	
	Adjusted odds ratios† (95% confidence intervals)							
Ever exposed	0.96	(0.68-1.34)	1.02	(0.74-1.41)	1.16	(0.76-1.75)	0.92	(0.66-1.27)
Lifetime cumulative dose‡								
1 st quartile	0.89	(0.49-1.55)	0.95	(0.52-1.67)	1.09	(0.48-2.28)	1.25	(0.72-2.09)
2 nd quartile	0.95	(0.52-1.65)	0.94	(0.52-1.63)	0.51	(0.17-1.21)	0.86	(0.46-1.52)
3 rd quartile	1.21	(0.69-2.05)	0.90	(0.51-1.53)	1.54	(0.81-2.81)	0.45	(0.21-0.89)
4 th quartile	0.80	(0.40-1.49)	1.33	(0.78-2.20)	1.47	(0.76-2.72)	1.18	(0.66-2.01)

* Reference category is 1,340 unexposed subjects (less than 1/30 Hygienic Effect [HE]).

† Odds ratios adjusted for age, sex, alcohol consumption, cigarette smoking, and consumption of paracetamol and aspirin.

‡ The product of the exposure intensity level (HE), exposure frequency (days per month) and duration (years) of the solvent exposure, summed over all work periods in the subjects occupational history.

5.2.3 Organic solvent exposure (Paper III)

The odds ratios for “ever solvent exposed” were close to unity for chronic renal failure associated with glomerulonephritis, diabetic nephropathy, renal vascular disease, and other renal diagnoses. Also, there was no clear trend in risk across dose levels of solvent exposure in any of the diagnostic groups (Table 16). Solvent exposure was evenly distributed between our control subjects that reported diabetes or hypertension, and control subjects not reporting these conditions (data not shown).

5.2.4 Occupation and workplace exposures (Paper IV)

In relation to the same three low-risk groups as in Table 13, manufactory workers ranked highest with regard to chronic renal failure associated with glomerulonephritis followed by subjects working in administrative, financial and clerical occupations, and those engaged in commercial work. The risk among transport and communication workers was no more than 14% higher than that in the low-risk groups (Table 17). The administrative, financial and clerical group had the highest risk diabetic nephropathy, but only slightly higher than among transport and communication workers, and subjects in service occupations. The risk for chronic renal failure due to renal vascular disease was highest among transport and communication workers, second highest among administrative, financial and clerical workers, and third highest among manufactory workers. With regard to risk of chronic renal failure due to systemic disease or vasculitis, the commercial work group ranked number one, the administrative, financial and clerical group ranked number two, while the transport and communications group ranked number three. The latter group stood out as the one with the highest risk for both chronic renal failure due to hereditary renal disease and “other renal chronic renal failure” (Table 17).

Table 17. Odds ratios and 95% confidence intervals for chronic renal failure (CRF) for main occupational group by type of underlying renal disease.*

Diagnosis group	Service occupations	Manufacturing work	Transport & communications	Commercial work	Administrative financial & clerical
Odds ratios [†] (95% confidence intervals)					
Glomerulonephritis	1.13 (0.57-2.15)	1.59 (1.02-2.49)	1.14 (0.52-2.35)	1.42 (0.79-2.50)	1.49 (0.88-2.49)
Diabetic nephropathy	1.67 (0.96-2.87)	1.51 (0.99-2.31)	1.69 (0.89-3.14)	1.09 (0.61-1.91)	1.70 (1.06-2.70)
Renal vascular disease	1.49 (0.63-3.29)	1.88 (1.08-3.34)	2.96 (1.34-6.37)	1.54 (0.70-3.24)	2.52 (1.31-4.86)
Systemic disease or Vasculitis	0.50 (0.13-1.91)	1.73 (0.79-3.76)	2.30 (0.72-7.32)	3.43 (1.52-7.73)	2.34 (1.04-5.30)
Hereditary renal disease	1.54 (0.63-3.49)	0.66 (0.32-1.35)	2.46 (0.95-6.01)	1.41 (0.61-3.04)	1.71 (0.87-3.31)
Other renal CRF	1.13 (0.44-2.63)	1.47 (0.75-2.86)	2.84 (1.17-6.64)	1.15 (0.47-2.58)	1.50 (0.71-3.10)

* Subjects with their main occupation falling in the (i) technical, scientific, humanistic, and artistic, (ii) health care and social, and (iii) agricultural, forestry, and fishing industry work categories constituted the reference group.

[†] Odds ratios and 95 percent confidence intervals adjusted for age, sex, smoking, alcohol consumption, regular use of paracetamol and/or aspirin, and occupational exposure to exhaust fumes, silica, wood dust, grain dust, textile fibre dust, cellulose dust, lead, mercury, chromium, cadmium, nickel, copper, tin, zinc, and organic solvents.

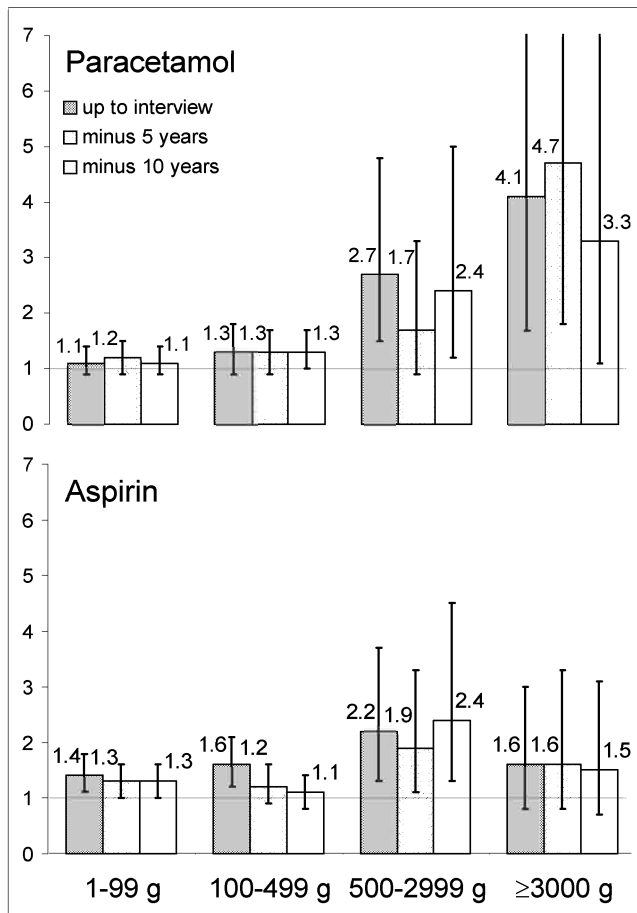


Figure 6. Odds ratios (and 95% CI) for chronic renal failure according to the cumulative lifetime dose of paracetamol or aspirin in analyses based on different periods of exposure. The odds ratios are for comparisons with nonusers of both classes of analgesics.

5.3 RESULTS BASED ON DIFFERENT PERIODS OF EXPOSURE

5.3.1 Analgesics use (Paper I)

Symptoms associated with renal disease may prompt the use of analgesics and the estimations of the associations between analgesic use and chronic renal failure may be distorted by reverse causation. Indeed, a greater proportion of patients than of controls subjects had begun to use analgesics regularly (35% vs. 25% for paracetamol and 37% vs. 28% for aspirin) within five years before the interview. We therefore performed additional analyses in which we disregarded the most recent exposure. If the associations between analgesic use and renal failure mainly represent the effect of increasing symptoms of renal failure these analyses would yield distinctly lower estimates of the associations. The odds ratios for chronic renal failure associated with regular paracetamol use

among subjects who did not use aspirin regularly, however, remained practically unaltered when exposure during the five or ten most recent years was disregarded, and only modest attenuation of odds ratios was seen for the corresponding regular aspirin use (Figure 6).

5.3.2 Organic solvent exposure (Paper III)

Analyses that disregarded the most recent 10 years revealed a pattern of no association between solvent exposure and chronic renal failure similar to that found in the initial analyses. This indicates that the absence of association was not mainly an effect of decreasing employability and organic solvent exposure opportunities with increasing renal failure among the case patients. Similarly, in analyses that only took the most recent 10 years of exposure into account, we found no increased risk of chronic renal failure associated with any measure of solvent exposure (data not shown).

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

The goal of all research is to obtain valid evidence regarding the hypothesis under study. Ideally, we would want the quality of evidence from observational research to be as high as that obtainable from a well designed experiment. In an experiment, however, the investigator has the power to assign exposures in a way that enhances the validity of the study, whereas in observational research the circumstances of exposure cannot be controlled. The investigator must rely heavily on the primary source of discretion that remains; the selection of subjects (Rothman & Greenland, 1998c). There is no such thing as a perfect method; each method has its strengths and weaknesses and experimentation may be unnecessary, inappropriate, impossible, or inadequate (Black, 1996). Non-experimental and experimental approaches should be seen as complementary; the question being asked determines the appropriate research architecture, strategy and tactics to be used (Sackett & Wennberg, 1997).

6.1.1 Study design

The two main epidemiologic study types are the cohort study and the case-control study. In this thesis, all four studies are parts of a large case-control study. For diseases that are rare, case-control studies become the only useful alternative. On the other hand, for exposures that are extremely rare, case-control studies are not efficient. Case-control studies also present more opportunities for bias and mistaken inference than cohort studies. Properly carried out, however, case-control studies provide information that mirrors what could be learned from a cohort study, usually in a more efficient way (Rothman, 2002).

In a case-control study, to assure comparability, cases and controls should be representative of the same base experience. The base is the set of persons or person-time in which diseased subjects become cases. Thus, the base is the members of the underlying *source population* for the cases during the time period when they are eligible to become cases (Wacholder et al., 1992a). When the cases are defined before the *study base* is identified, sampling of adequately comparable controls may become difficult. Correspondingly, when the population experience is geographically and temporally defined by the targeted population, sampling of controls is easy but the necessary complete identification of cases may become difficult (Wacholder et al., 1992b).

In our population-based study the base was well defined. The Swedish national registration numbers and the continuously updated population register permitted strict random sampling of population controls, independently of exposure status. Our comprehensive organization for case ascertainment, including both monitoring via essentially all medical laboratories and via contact persons at all nephrological and relevant medical departments, was set up to insure against important deficiencies in case ascertainment and recruitment. The true incidence of overall chronic renal failure is unknown but an estimate of the overall chronic renal failure incidence rate on the basis of this study would be 115 patients per million people (pmp) per year. This is lower than the inci-

dence of renal replacement therapy in Sweden [118, 121 and 124 pmp per year during 1996, 1997 and 1998, respectively (SRAU, 2001)] and may indicate incomplete identification of cases. A higher incidence of renal replacement therapy in Sweden among persons older than 75 years or born outside of Sweden may partly explain why chronic renal failure incidence in our study was lower than the incidence of renal replacement therapy. Furthermore, differences in diseases underlying chronic renal failure contribute to the apparent low incidence in comparison with renal replacement therapy; we excluded patients with pre- or post-renal disease. Seven to 8% of all patients who started on renal replacement therapy between 1991 and 1999 had an underlying renal disease diagnosis that was incompatible with inclusion in this study (SRAU, 2001).

6.1.2 Validity

Internal validity is the validity of the conclusions drawn as they attribute to the members of the source population, while external validity is the validity of the conclusions as they attribute to people outside the source population (*generalizability*). Internal validity is a prerequisite for external validity (Rothman & Greenland, 1998b). Systematic error or *bias* can detract from internal validity and has to be considered in the design and analysis of studies.

Selection bias

Selection bias is a systematic error that stems from the procedures used to select subjects and from factors that influence study participation (Rothman, 2002). Selection bias may have been introduced in our study; since non-participation, particularly which attributed to active refusal, may be unevenly distributed across levels of exposure, and since the refusal rate was higher among our control subjects than among our case patients. Although this may have inflated the observed associations, the difference in participation rates between cases and controls, however, is not large enough to entirely explain our positive findings. Differential disease detection or case ascertainment in relation to exposure may also introduce bias. The objective diagnostic criteria that defined incident cases who permanently passed a pre-defined serum creatinine level sufficiently low to insure that most cases had not reached end-stage renal disease, minimizes selective loss of patients with rapid disease progression and early death. At the same time, the serum creatinine level was sufficiently high to avoid the possible bias linked to detection of clinically silent disease (co-morbidity or other circumstances leading to a higher probability for serum creatinine testing). Serum creatinine testing was carried out for overt symptoms in routine clinical practice and not as a screening effort among symptomless people. This should allay concerns about possible selective recruitment from a pool of subjects with prevalent disease. Different disease detection among subjects in different socio-economic groups would have biased the results in our study on socio-economic status and chronic renal failure (Paper II). This would, however, probably have resulted in earlier diagnosis among socio-economically privileged people, thus counteracting the observed inverse relationship. Furthermore, ascertainment bias is unlikely, given the equal access at a low cost for everyone to Swedish health care (Calltorp et al., 1996), and the essentially complete coverage by our case-finding organization.

Information bias

Systematic error in a study can arise because the information collected about or from study subjects is erroneous and incorrectly categorized (*misclassified*) (Rothman, 2002). Any measurement errors that are different among subjects with and without disease are a greater threat to the study's validity than non-differential ones, since the direction of bias in the effect estimate may be away from the null and may be difficult to predict (Kopec & Esdaile, 1990). Thus, retrospective exposure assessment is a potential weakness of case-control studies and a discrepancy in recall or reporting between cases and controls involving *differential* exposure misclassification, introduces *recall bias* that may contribute to spurious associations. In the study of analgesics use [Paper I (Fored et al., 2001)], we used photographs of products and their packaging to improve the reliability of subjects' recall (West & Strom, 1994). Blind assessment of exposure most effectively ensures comparability of measurement (Kopec & Esdaile, 1990). As usually is the case in studies of slowly progressing chronic diseases, blinding the interviewers to the case or control status of subjects in our study was deemed impossible. However, the interview covered a multitude of exposures, and interviewers were unaware of the study hypotheses. Moreover, they were trained to follow the questionnaire carefully in a standardized manner regardless of the subject's case or control status.

Poor recollection of previous exposures among both cases and controls, or inadequate instruments for exposure assessment introduces random *non-differential* misclassification which tends to bias any associations towards the null. We regard the possibility of misclassification of socio-economic status level [Paper II (Fored et al., 2003)] or main occupational group (Paper IV) following incomplete recollection of previous occupations unlikely. Non-differential misclassification is a greater concern in interpreting the studies that seem to indicate the absence of an effect. In our studies of workplace exposures (Paper III and IV), detailed data about occupations, specific tasks associated with exposure, and exposure information obtained in an initial interview and a follow-up interview, were evaluated by an expert occupational hygienist. This ambitious expert rating procedure is considered to be a valid approach in the context of a population-based study (Siemiatycki et al., 1997) and should reasonably have resulted in a lower degree of misclassification than in several previous case-control studies.

Confounding

Confounding may be regarded as a mixing of effects. A confounding factor must have an effect and must be imbalanced between the exposure groups to be compared. Thus, a confounder must be associated with the disease and must be associated with the exposure, but must not be an effect of the exposure (Rothman, 2002). In experiments, randomization aims to prevent confounding for unknown factors as well as for factors that are already a concern. The methods available to prevent confounding in the design of non-experimental studies are restriction and matching. In our study, we restricted subjects to be native Swedes in order to prevent confounding by ethnicity in our analysis of the effect of low socio-economic status on chronic renal failure development (Paper II). Subjects were frequency-matched for sex and age (in 10-year strata). Matching in case-control studies, however, does not prevent confounding and may in fact introduce bias (Rothman & Greenland, 1998a). The matching in our study forced the controls to have the same distribution of sex and age as the cases across strata and hence prevented extreme departures from what would be the optimal control distribution. In this way

matching afforded an enhanced efficiency for the control of confounding (Wacholder et al., 1992c). An advantage in case-control studies is the opportunity to include adequate information on several possible confounding factors of concern. In the data analysis, confounding from these factors can be managed by the use of either stratification or regression models. As previously described in the methods section, we analysed the data using regression models to control for other possible confounders including the frequency-matching variables.

Confounding by indication or Protopathic bias

Typically, there are differences in disease severity or other risk factors between populations who receive different treatments. Those who take a drug generally differ from those who do not according to the medical indication for which the drug was prescribed. These differences introduce a bias in the comparison that is called *confounding by indication* (Rothman, 2002). Thus, the medical indication of drug use is a disease per se and not the severity of its manifestation. Correspondingly, the symptoms of diseases that predispose patients to renal failure may lead to an increased use of analgesics, thus possibly introducing a bias into our assessment of the effects of analgesics (Paper I). In this case, when the first symptoms of the outcome of interest may be the reasons for use of treatment, the term *protopathic bias* [~ first experience, suffering; *Greek* (The Merriam-Webster OnLine Dictionary, 2002)] has been proposed as a more accurate designation (Salas et al., 1999).

Confounding by indication and protopathic bias, unfortunately, is only partly amenable to the standard methods of design or analysis as described above. We found no indications that the severity of the renal failure affects analgesic consumption. Further, the associations between the use of analgesics and the risk of chronic renal failure were not consistently stronger among subjects with underlying diseases causing frequent aches and pains. In our study, the analgesic exposure was well-defined in terms of timing, dose and duration of use. This allowed us to try and separate analgesic use of causal importance from that possibly triggered by symptoms of renal disease by performing lagged time analyses. A reduction in the estimates of relative risks in these analyses in which analgesic use during the 5 and 10 years before the interview was disregarded would indicate that reverse causality explained the associations, at least partly. We found minor reductions in the estimates of relative risk. However, recall of analgesic exposure decreases over time, thus inherently tending to attenuate relative risk estimates from the distant past. Furthermore, lagged analyses must be interpreted cautiously (Goldfarb & Henrich, 1998; Moulton & Le, 1991; Perneger et al., 1995a), particularly when any potential latency time between analgesic exposure and chronic renal failure is unknown. The analgesics could conceivably act anywhere in a possibly long-lasting multi-step process. The latency might be short if analgesic exposure were to decompensate or promote a previously stable renal disease.

6.1.3 Precision

Precision in measurement and estimation corresponds to the reduction of random error, which is actually nothing more than variability in the data that we cannot readily explain (Rothman, 2002). A variety of design aspects affect study efficiency and in turn affect the precision of study results. These factors include the proportion of subjects exposed,

the proportion of subjects who have or will develop disease, and the distributions of subjects according to key variables, such as confounders and effect modifiers, which must be taken into account in the analysis (Rothman & Greenland, 1998b). While the point estimate describes the strength of a relation, the confidence interval indicates the precision. To have a clear interpretation of data, separate information on both is important.

The P-value function curve readily provides a quantitative overview of the statistical relation between exposure and disease. It indicates the best single value for the relative risk, and it gives a visual appreciation of the degree of precision of the estimate (Rothman, 2002). The curve in Figure 4 plots the P-values testing every possible value of the relative risk of chronic renal failure among regular paracetamol users (Table 7). The impression is that the risk estimate is relatively strong and the precision adequate.

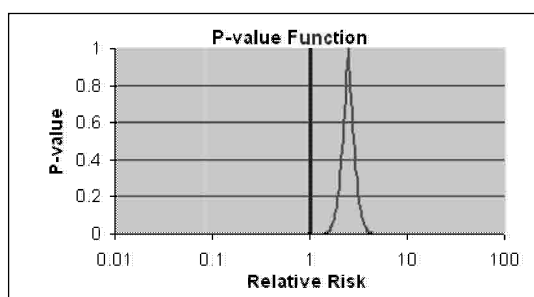


Figure 4. P-value function curve for the data on regular paracetamol use in Table 7.

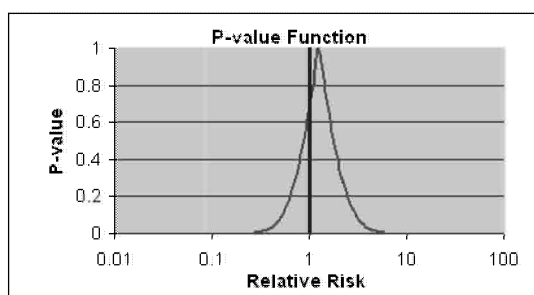


Figure 5. P-value function curve for the data on cadmium exposure in Table 12.

A disadvantage of the case-control approach is poor precision of relative risk estimates pertaining to exposures with low prevalence in the population. Several of the occupational exposures belong in this category and our null findings regarding lead, mercury, chromium and grain dust exposure need to be cautiously interpreted (Paper IV). Our data confirmed the well-established association between cadmium exposure and renal damage, however, with a low precision (Figure 5).

6.2 FINDINGS AND IMPLICATIONS

6.2.1 Paracetamol and aspirin use (Paper I)

In our study on the use of analgesics, regular use of either paracetamol or aspirin or of both was associated in a dose-dependent manner with an increased risk of chronic renal failure. These results are in concert with the previous population-based case-control studies (Perneger et al., 1994; Sandler et al., 1989). The odds ratios among regular users exceeded 1.0 for all diagnostic types of chronic renal failure, albeit not always significantly. The regular use of other non-narcotic analgesics than paracetamol and aspirin was not associated with an increased risk of chronic renal failure in general.

Pre-existing renal or systemic disease was present in all our patients, suggesting that such disease has an important role in causing analgesic-associated chronic renal failure. In a recently published study (Rexrode et al., 2001), subjects with such pre-existing conditions were unlikely to be recruited, and the findings indicate that persons without pre-existing disease who use analgesics have only a small risk of end-stage renal disease.

I believe that this study by way of the well-reasoned design, the thorough ascertainment of case patients, and the implementing of structured personal interviews, approaches the limits of what can be achieved in a case-control study. It is, however, impossible to rule out bias, in particular protopathic bias, inflating the estimates of relative risk. Furthermore, bias may have affected the estimates differently for paracetamol use and aspirin use. It is conceivable that symptoms associated with progressing renal disease resulted in increased indications for the use of paracetamol. The same indications may also have resulted in the use of aspirin. There is, however, another common indication for aspirin medication; the prevention of thrombosis in vascular disease. Unfortunately, we were unable to separate the use of aspirin by these different indications. Consequently, the estimates of relative risk for the development of chronic renal failure pertaining to regular aspirin use may be distorted by 'proper' confounding by indication in addition to protopathic bias. The small difference in attenuation of risk estimates between paracetamol and aspirin use in our analyses based on different periods of use, may reflect this different distortion.

Paracetamol use and aspirin use had similar effects on the overall risk of chronic renal failure. This lack of specificity might suggest non-causal associations. However, lack of specificity must be interpreted cautiously because renal failure probably has multiple component causes and because misclassification of the specific causes of renal failure may result in spurious associations for some renal failure causes truly unrelated to the exposure (Perneger et al., 1995a). Furthermore, in experiments in animals, both analgesics have induced irreversible renal injury (Nanra & Kincaid Smith, 1993; Sabatini, 1996). The only prior investigation of analgesic exposure and pre-uraemic cause-specific renal failure also found elevated risks for practically all underlying causes of chronic renal failure (Sandler et al., 1989). If analgesics act independently of these underlying conditions, moreover, absence of variation across different causes of renal failure would be expected. In addition, increased risks were not observed with analgesics other than paracetamol and aspirin.

The low prevalence of recalled phenacetin use (2%) may reflect underreporting and would hinder adequate statistical adjustment for confounding from phenacetin on the chronic renal failure risk of other analgesics. Any important influence of phenacetin, however, seems improbable in our study since analgesic mixtures containing phenacetin practically disappeared from the Swedish market in 1961 when its sale was restricted (Buckalew Jr & Schey, 1986). The very few patients in our study diagnosed as having analgesic nephropathy diagnosis suggests either that this condition has become rare among newly diagnosed chronic renal failure patients in Sweden (Noels et al., 1995) or that these patients may have received other diagnostic labels (Wing et al., 1989).

Most of our results are consistent with a moderately strong contributory role of paracetamol and – somewhat less certain – aspirin in the development of chronic renal failure, practically regardless of accompanying pathology.

6.2.2 Low socio-economic status (Paper II)

Household socio-economic status emerged as a significant risk indicator for chronic renal failure, independently of factors such as age, sex, body-mass index, cigarette smoking, alcohol consumption, and use of aspirin or paracetamol. The risk gradient from highest to lowest socio-economic stratum was similar for diseases as different as diabetic nephropathy, glomerulonephritis, and renal vascular disease, but the detailed trend pattern varied with underlying pathology.

To our knowledge, this study is the first to examine the influence of socio-economic status on chronic renal failure before end-stage. In prior studies (Klag et al., 1997; Perneger et al., 1995b; Young et al., 1994), limited to the association between socio-economic status and renal replacement therapy among patients with end-stage renal disease, the results may have been affected following changes in measures of socio-economic status due to reverse causation. As opposed to the aggregated socio-economic status indices (area-based measures of education or income), or socio-economic status measured as current income (which may have changed as a result of the disease), we classified our subjects individually, according to the highest socio-economic status level attained during a life-time. To classify a subject's socio-economic status, we used the Swedish socio-economic classification scheme, primarily based on the occupation (SEI, 1982). Evaluations have shown that this scheme performs well in comparison with other classifications (Andersson et al., 1981; Lundberg, 1991). An element of judgmental categorization is, however, inherent in occupation-based classifications of socio-economic status (Liberatos et al., 1988).

Socio-economic status per se does not plausibly affect renal function and cannot be regarded as a specific exposure but a marker for general and cultural circumstances. Biologically meaningful exposures associated with socio-economic status are likely to explain most or all of the relationship with chronic renal failure. Control for several factors with known or suspected impact on renal function (including analgesic use) did not cancel the inverse relationship between socio-economic status and chronic renal failure. Other factors that may explain the association include other chronic diseases, diet and occupational exposures. Although the prevalence of hypertension and diabetes was higher among low socio-economic status individuals in some studies (Colhoun et al.,

1998; Connolly et al., 2000), these ailments were essentially evenly distributed across socio-economic status levels in our study. A diet low in fruit and vegetables has been implicated in the aetiology of cardio-vascular disease (James et al., 1997) and may conceivably also affect the kidneys. Exposure to nephrotoxins occurs more often in occupations associated with lower socio-economic status (Wedeen, 1997). In our analyses of workplace exposures (Paper III and IV) no associations between exposure to several previously suggested agents and chronic renal failure were found and the risk associated with either silica dust or cadmium exposure cannot explain our findings regarding socio-economic status. Further, the fact that household socio-economic status tended to be more strongly linked to chronic renal failure risk than individual socio-economic status might indicate that the association can be attributed more to issues related to lifestyle and cultural factors than to occupational exposures. Moreover, accumulating evidence suggests that social status itself, regardless of associated material and economic advantages may confer health benefits possibly via psychosocial mechanisms (Fitzpatrick, 2001).

6.2.3 Organic solvent exposure (Paper III)

In our study, exposure to organic solvents in general was unrelated to risk of chronic renal failure of all diagnostic types. Our results are at odds with the findings in several previous case-control studies (Bell et al., 1985; Finn et al., 1980; Nuyts et al., 1995; Porro et al., 1992; Ravnskov et al., 1979; Ravnskov et al., 1983; Steenland et al., 1990; Yaqoob et al., 1992; Yaqoob et al., 1994a; Yaqoob et al., 1994b; Zimmerman et al., 1975) and challenge the present view that organic solvent exposure importantly attributes to end-stage renal disease development (Ravnskov, 2000a). In contrast to the careful design of our study, several of the previous studies were hospital based (Bell et al., 1985; Porro et al., 1992; Ravnskov et al., 1979; Stengel et al., 1995; van der Laan, 1980; Yaqoob et al., 1992; Zimmerman et al., 1975) or had control selection procedures that did not guard against influence of solvent exposure status, or could not assure that cases and controls represented the same study base (Wacholder et al., 1992a). Moreover, several previous studies concerned patients with end-stage renal disease (Finn et al., 1980; Steenland et al., 1990; Yaqoob et al., 1992; Zimmerman et al., 1975), and may have been less resistant against selection and recall bias than our study.

While recall bias seems a very unlikely explanation for our negative findings, it is conceivable that differential recall among cases and controls in previous positive case-control studies may have contributed to spurious associations. In order to negate a true positive association between solvent exposure and chronic renal failure risk, our case patients would have had to systematically underreport their exposure, or our occupational hygienist would have had to systematically underreport the exposure of the cases. Likewise, negative confounding cannot readily explain our null results. It is possible, though, that those individuals with conditions known to predispose for chronic renal failure were advised to refrain from organic solvent exposure, or to choose different occupations, following the reports from earlier studies. Such negative confounding by underlying disease, however, could not explain the absence of association with chronic renal failure due to glomerulonephritis, since this disorder is not preceded by any known predisposing disease.

Severe non-differential exposure misclassification could theoretically turn a true association into a null result (Rothman & Greenland, 1998b). We believe that the thorough and individual assessment of solvent exposure in our study reduced the potential for non-differential exposure misclassification. Exposure assessment has varied in the previous studies. In the very first investigation published (Zimmerman et al., 1975), the exposure scores used were poorly defined. The exposure score developed by Ravnskov et al. (Ravnskov et al., 1979) and later used in several studies (Bell et al., 1985; Porro et al., 1992; van der Laan, 1980; Yaqoob et al., 1992; Yaqoob et al., 1994a; Yaqoob et al., 1994b), represents an improvement but the assessment scale with exposure intensity factors according to 17 pre-defined occupational activities was crude and may have led to varying degrees of misclassification.

Most organic solvents consist of a mixture of several different compounds and organic solvent exposure often entails exposure to several different mixtures and compounds. We chose to assess organic solvent exposure overall to avoid the uncertainties of retrospective assessment of the different subclasses of organic solvents. Accordingly, any associations between possibly more nephrotoxic subclasses of solvents and CRF may have remained undetected. In general, the levels of exposure in our study possibly were low, compared to previous studies. The high solvent exposure level included exposures from 30% of the occupational exposure limit or more, and subjects with the heaviest exposures may actually have had relatively low exposures. Since this study was designed to investigate the association between solvent exposure and chronic renal failure in general, an effect on specific subtypes of renal disease may have remained undetected because of possible diagnostic misclassification or inadequate statistical power. Consequently, detrimental effects from very high exposure organic solvents overall or to certain subclasses of solvents, or on specific renal diseases may have remained undetected. A population-based case-control study is, however, the preferred design of a study of risk factors for a rare disease, and will provide a better picture of the impact of exposure on the overall incidence of chronic renal failure in the population.

6.2.4 Occupation and workplace exposures (Paper IV)

We found substantial variation in risk of pre-uraemic chronic renal failure across occupational groups, unexplained by lifestyle factors with known links to chronic renal failure risk or by occupational exposures implicated in the literature (Nuyts et al., 1995; Wedeen, 1997). After adjustments for all these factors, subjects falling in the (i) manufacturing, (ii) administrative, financial, and clerical, and (iii) transport and communication work categories had significant 1.5-fold, 1.7-fold and 1.8-fold risk elevations, respectively, compared with subjects in the work categories with the lowest risks. The magnitude of the gradient and the ranking of the different occupational groups varied somewhat with disease-specific type of chronic renal failure, but high risk occupational groups tended to have a high risk for most chronic renal failure types.

The relations between renal disease and occupational exposures, other than organic solvents, have been investigated in two previous case-control studies (Nuyts et al., 1995; Steenland et al., 1990). The study by Steenland et al. was limited to male patients diagnosed with end-stage renal disease and patients with a renal disease known to have a non-occupational cause were excluded. In the population-based study by Nuyts et al. the

response rate among the chronic renal failure patients was high but, on average, two controls had to be invited before one accepted to participate. We used the same thorough and individual assessment of exposure as in the study on solvent exposure. In the study by Steenland et al., exposure level was not considered for the occupational exposures other than solvents. Exposure assessment in the study by Nyuts et al. did not materially differ from ours, except that the exposure levels did not relate to the occupational exposure limit of each pollutant, and their interviews were less exhaustive.

The prevalence in the population of several of the exposures was low resulting in poor precision of the relative risk estimates. Our null findings regarding lead, mercury, chromium and grain dust are at odds with the study by Nyuts et al., and even though our data clearly contradicts the more than 2-fold excesses reported in this previous study (Nyuts et al., 1995), our results need to be interpreted cautiously. Previous reports suggesting that silica dust is an important risk factor for chronic renal failure (Steenland et al., 2001; Stratta et al., 2001) are confirmed in our study, as was the well-established association between cadmium exposure and renal damage (Jarup et al., 1998). However, in view of the low exposure prevalence and the absence of striking excesses, the etiologic fractions (Miettinen, 1974) are reasonably small. Low exposure prevalence may in turn be attributed to the preventive measures introduced in Swedish workplaces.

The substantial variation in chronic renal failure risk across occupational groups is unlikely to be explained by self-selection into certain occupational groups of persons with emerging chronic renal failure. Most people choose their occupation early in life, long before any signs of chronic renal failure or its antecedents are expected, and changes of occupational group are uncommon. Notwithstanding, in our control group we found diabetes to be somewhat over-represented among manufactory workers (data not shown) and this could explain in part the association with diabetic nephropathy. Similarly, an overrepresentation of self-reported hypertension among controls in the manufactory and administrative/financial/clerical groups could potentially explain the elevated risk for renal vascular disease in these occupational groups.

The evident variation in chronic renal failure risk across occupational groups may be due to yet undisclosed nephrotoxic exposures in workplaces. The factor(s) responsible may, however, not necessarily be work-related. Clearly, the occupational groups used in our study have certain socio-economic implications, and the observed risk pattern does fit well with socio-economic factors as the main determinants. Most of the effects of socio-economic status on disease risks in general have traditionally been attributed to lifestyle and occupational exposures with known biological effects. In the case of chronic renal failure, occupational exposures and smoking are candidates, exposures that were controlled for in this investigation. There are also unexplained effects of socio-economic status, possibly mediated via psychosocial factors such as mental stress and/or high demands in combination with low autonomy (Levi et al., 2000), which has potential impact on the cardiovascular system (Kivimäki et al., 2002), and which may possibly be relevant also in the aetiology of renal vascular disease [Paper II (Fored et al., 2003)].

6.3 FUTURE RESEARCH

Over-the-counter analgesics such as paracetamol and aspirin are easily accessible, widely used and are sold in large quantities. Even a relatively small detrimental effect on renal function from the use of these analgesics would have considerable implications. Therefore, it is important to disentangle if and to what extent these analgesics cause renal injury, even though this may seem like an insurmountable and unfeasible task with the research methods presently at hand. Any suggestions?

Identification of adverse drug reactions associated with long-term administration of drugs for chronic diseases is problematic (Brewer & Colditz, 1999). At the same time, there is an increasing need for effective methods in post marketing surveillance of new potent and possibly harmful medications of chronic diseases. Systematic data exploration in otherwise similar populations of medication users and nonusers may be undertaken to look for adverse drug reactions, using epidemiological research methods.

Is renal failure a disease of the disadvantaged and can this cause be prevented? Even in Sweden, a country with fairly egalitarian socio-economic policies (Adler & Ostrove, 1999) and with a strong commitment to equity of health care access and use (Calltorp et al., 1996), we found an inverse relation between socio-economic status and chronic renal failure. The search for biologically meaningful exposures associated with socio-economic status is important. Variations in diet across socio-economic levels may be a valid hypothesis. Secondary analyses of the MDRD study indicate a beneficial effect on the progression of chronic renal disease (Levey et al., 1999). Is a diet with high levels of protein a risk factor for renal disease? Does the amount of protein intake vary with level of socio-economic status? Socio-economic disparities in foetal environmental factors and pregnancy outcome are other conceivable factors that warrant further studies (Hoy et al., 1999; Kramer et al., 2000; Merlet-Benichou et al., 1999; Robinson, 2001).

More research is warranted about the possible conglomerate of yet unidentified risk factors of chronic renal failure related to different occupational groups. The effects of these factors can be discerned through the study of occupational group-specific risks for chronic renal failure. By the results of our data, the etiologic fractions attributable to these putative factors in the manufactory, transport/communication and administrative/financial/clerical occupational groups are each approximately 4%, 2% and 4%, respectively. The search for these factors includes new workplace exposures as well as psychosocial factors and other exposures also associated with socio-economic status. Case-control studies nested within large enough cohorts of subjects in certain occupational groups may be an accessible way to perform these studies.

The impact of epidemiological research in nephrology is growing. Epidemiology has already contributed to nephrology, particularly in the identification of risk factors for the development of renal failure and has helped establish preventive actions (Elseviers & De Broe, 2001). The chronic renal failure patients in the ORFAN-study form a well-defined cohort in which the effect of a plentitude of exposures on the progression of renal failure can be investigated. Studies in which our comprehensive and carefully collected data is linked with existing Swedish health care registries have excellent prospects of increasing the present knowledge on causes of renal disease.

CONCLUSIONS

Our results are consistent with the existence of exacerbating effects of paracetamol and aspirin on chronic renal failure. However, it is impossible to rule out bias caused by the consumption of these analgesics for symptoms of the conditions that predisposed patients to renal failure.

Despite negligible inequalities in access to health care in Sweden, and a tentatively limited range of exposure to factors related to socio-economic status and with a potential impact on renal function, socio-economic status appears to represent an independent risk indicator for chronic renal failure in Sweden.

The results from our study do not support an adverse effect of organic solvents exposure on the development or progression of chronic renal failure in general. Detrimental effects from high exposure to certain subclasses of solvents, or on specific renal diseases cannot be ruled out. Our results, however, indicate that the etiologic fraction of solvent exposure on chronic renal failure, if any, would be small.

Due to the low exposure prevalence and the absence of striking excesses, the etiological fraction attributed to each of the implicated exposure agents, including exhaust fumes, organic dusts, lead, mercury, and chromium, is likely to be small in Sweden. Previous reports of cadmium and silica dust being important risk factors of renal damage were confirmed. A significant variation in chronic renal failure risk across occupational groups could not be explained by studied lifestyle factors, analgesics use or workplace exposures.

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