In 1996, Li et al. reported a strong, statistically significant association between maternal smoking during pregnancy and urinary tract malformations. The study was based on a rather small data set where information on maternal smoking habits was gathered retrospectively with a response rate of only 65%. In some earlier studies, the group of urinary organ malformations and malformations of the genital organs were combined. These two main groups of malformations are not believed to be related to each other from an aetiologic point of view, and in no study combining those groups was a significant effect of maternal smoking demonstrated. A positive association between maternal smoking and certain specific birth defects has earlier been reported by some investigators: oral clefts, and limb reduction defects. In order to study if the association between maternal smoking and urinary organ malformations found by Li et al. could be confirmed, the Swedish medical registries were used to obtain a large and reliable data set.

**MATERIAL AND METHODS**

In all, 1202 infants with urinary tract malformations, born 1983–1993, were identified from two registries: The Swedish Registry of Congenital Malformations (RCM), and the National Board of Health Medical Birth Registry. These registries have been described in detail elsewhere. The Medical Birth Registry contains medical information on nearly all deliveries in Sweden (coverage about 99%). All diagnoses are given as ICD codes (1983–1986: a Swedish modification of ICD-8 containing five digits and therefore more specific than the international ICD-8, and 1987–1993: ICD-9). Since 1983 this registry contains information on maternal smoking habits in early pregnancy. This information is collected on forms used at all antenatal clinics. Nearly all women avail themselves of the free antenatal service. At the first visit (usually during week 10–12), each woman is interviewed by a midwife and, among other things, the smoking habit of the woman is stated as none, or cigarettes per day. Smoking information is available for 93% of all women.

The Registry of Congenital Malformations covers the whole country and all diagnoses (after consultation of relevant documents e.g. copies of x-ray or post mortem reports) are given in a special five-digit code (more detailed than the standard ICD code). The registry is based on diagnoses obtained during the first week of life and reported within 6 months. Each case is identified with the personal identification number of the mother and the date of birth of the infant. This makes it possible to link this registry with the Medical Birth
Registry so that, e.g. information on maternal smoking habits can be obtained.

Confusion exists concerning the definition of certain forms of renal maldevelopment, especially the cystic forms of dysgenesis. According to the Committee on Classification, Nomenclature and Terminology, Section on Urology, American Academy of Pediatrics,\textsuperscript{17} multicystic kidney disease is a variation of dysplasia, and the term polycystic disease refers to two certain genetic disorders: infantile polycystic kidney disease and adult polycystic disease. Thus, in this study, renal cystic disease was divided into genetic (polycystic) and non-genetic (dysplastic/multicystic) cases.

All cases of urinary organ malformations were divided into two main groups and 10 subgroups:

Kidney Malformations
(ICD codes 7530, 7531, or 7533) with or without other malformations of the urinary organs)
A: Kidney agenesis/hypoplasia.
B: Kidney dysplasia (including multicystic kidneys).
C: Horseshoe kidney or other kidney ectopia.
D: Autosomal recessive, autosomal dominant polycystic kidney disease, and cystic kidneys associated with multiple malformation syndromes (e.g. Meckels syndrome).
E: Unspecified renal cystic disease: no detailed post-mortem report was available in the RCM.
F: Unspecified kidney malformations.

Other Urinary Tract Malformations
(ICD codes 7532, 7534–7539 with no primary involvement of the kidneys)
I: Hydronephrosis (ICD-9:7532).
J: Other urinary tract malformations.

Cases with urinary organ malformation(s) together with another malformation, not involving the urinary organs, were classified as associated.

All infants with a known chromosome abnormality (n = 32) or with unknown smoking exposure in early pregnancy were excluded from the study. The reference group contains all births.

All odds ratios (OR) in this report were calculated using Mantel-Haenszel’s technique.\textsuperscript{18} Stratification was made for year of birth, maternal age (5-year classes) and parity (previously born infants +I [1, 2, 3, 4+]) and 95% confidence intervals (CI) were estimated using Miettinen’s method.\textsuperscript{19} When comparing two stratified OR, two-tailed z-tests were carried out, using the same variance as used to estimate the 95% CI.

RESULTS
Table 1 shows the size of the reference group and cases, the latter by site, presence of a non-urinary organ malformation (associated), and maternal smoking habits in early pregnancy. The OR for any maternal smoking were calculated for all main groups and subgroups and are also shown in Table 1. A moderate, statistically significant, increased OR for maternal smoking among infants with kidney malformations is shown, whereas for other urinary tract malformations, no association with maternal smoking is demonstrated. The OR for maternal smoking is of the same magnitude in the kidney agenesis/hypoplasia and dysplasia groups. No association between maternal smoking and genetic polycystic disease or horseshoe kidneys could be detected. If the genetic cases of kidney malformations are excluded, the OR for maternal smoking among cases of kidney malformations change to 1.23 (95% CI : 1.01–1.51), 1.37 (95% CI : 1.03–1.81), and 1.11 (95% CI : 0.84–1.49) for all, isolated, and associated cases, respectively. A stronger effect of smoking on isolated than associated cases of kidney malformations is indicated, but the difference between the OR may well be random (P = 0.47 or P = 0.30 if genetic cases are included or not, respectively). The only individual group that shows an obvious dose-response trend is the unspecified cystic disease group (in which most cases suffer from multicystic kidney disease and thus belong to the dysplastic group). However, for all kidney malformations (Total), a weak dose-response trend is indicated, but this may well be random (P = 0.62).

Among infants with kidney malformations 63% are males. Among male infants with kidney malformations the OR for maternal smoking is 1.39 (95% CI : 1.09–1.78), whereas among females the corresponding OR is 0.91 (95% CI : 0.64–1.29). Thus a differential susceptibility to maternal smoking between female and male fetuses is indicated, but the difference between the OR among males and females may be random (P = 0.06).

DISCUSSION
When investigating a possible teratogenic effect of a substance, it is important to make a distinct division into reasonably homogeneous subgroups of malformations to study. Otherwise a true teratogenic effect on a specific malformation may go undetected. On the other hand, if the possible teratogen is believed to be of not more than moderate strength, a large data set is needed to detect the putative teratogenic effect. Few investigators have had data sets with enough cases of specified urinary organ malformations to satisfy both demands. In a number of studies,\textsuperscript{2–5} urinary organ and genital organ
Malformations have been combined. Other investigators have chosen to make a division into subgroups even if the numbers of cases in each group have been small, and they did not detect any association between kidney malformations and maternal smoking during pregnancy.

In a study of 118 cases, Li et al. computed an OR of 2.3 (95% CI: 1.2–4.5) for all urinary organ malformations. For multicystic renal dysplasia (n = 10), a crude OR of 4.9 was reported. No results from further analysis after division into cases with or without involvement of the kidneys were reported.

In the present study, no difference between the OR for maternal smoking among cases of kidney agenesis/hypoplasia and dysplasia could be seen. The distinction between renal agenesis/hypoplasia and renal dysplasia can be difficult, and requires a detailed pathology report. As some cases of kidney malformations may be wrongly diagnosed, a true difference between the groups may be hidden. However, in 1996 Schuchardt et al. found evidence that defects in the ureteric bud could account for both renal agenesis and hypodysplasia in mice.

A possible mechanism for maternal smoking causing kidney malformations could be that cigarette smoking disturbs either the development of the ureteric bud, or the interaction between the ureteric bud and the metanephric mesenchyme. Maternal smoking is unlikely to affect monogenic conditions, and in the present study no association between smoking and renal polycystic disease was seen. The group of unspecified cystic kidneys is likely to contain some undetected genetic cases. Thus the weaker association, indicated in the present study, between maternal smoking and unspecified cystic kidneys than with renal dysplasia, is expected.

Li et al. found a stronger association between associated urinary tract malformations than isolated cases, a finding that could not be confirmed in the present study. As the ratio between associated urinary tract malformations and isolated cases in the former study differs considerably from the corresponding ratio in the present study (97:15 and 349:853, respectively), the American study may have included cases with multiple urinary tract malformations in the ‘associated’ group. Further, Li et al.
found a stronger association between urinary tract malformations and light smoking than with heavy smoking, and this was more apparent among female than male offspring. Those results are opposite to the findings of the present study where a weak dose-response effect was indicated and the association between kidney malformations and smoking was seen only among male offspring.

The literature on the aetiology of urinary organ malformations is limited which makes it difficult to trace possible confounders causing the results of this study. As a positive correlation between smoking and drinking is likely to exist, alcohol could be a confounder of particular interest. Clarren and Smith\(^2\) found that kidney hypoplasia/dysplasia occasionally (no numbers were given) occurred with fetal alcohol syndrome, but Li et al.\(^1\) found no significant association between maternal alcohol use and urinary organ malformations.

Many urinary tract malformations do not give symptoms until late in life and will not be included in the present study, based on case detection during the first few weeks of life. Also severe urinary tract malformations may go undetected if no autopsy is made in case of infant death. The prevalence of renal agenesis/dysgenesis found in this study (2.9 in 10 000 births) is in the upper span of the rates reported by different programmes in the International Clearinghouse for Birth Defects Monitoring Systems.\(^3\) Thus a comparatively high ascertainment of kidney agenesis/dysgenesis in the Swedish system is indicated, but the recorded rates are also affected by various degrees of inclusion or exclusion of renal dysgenesis.

The present study supports the findings of Li et al.\(^1\) of a positive association between maternal smoking and urinary tract malformations, but the OR found in the present study was only half of that found in the study with a smaller number of cases. The only demonstrated association in the present study was a positive association between kidney malformations and maternal smoking. No association between smoking and other urinary organ malformations was found. As expected, if the association between kidney malformations and maternal smoking is causal, no association between maternal smoking and monogenic polycystic kidney disease was indicated.

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