Received: 19 May 2022 | Revised: 3 September 2022 | Accepted: 28 September 2022

DOI: 10.1111/aogs.14473

ORIGINAL RESEARCH ARTICLE

New insights into smoking and urinary tract infections during pregnancy using pregnancy-pair design: A population-based register study

Hanna P. Wallin[1,2] | Mika Gissler[3,4,5] | Päivi E. Korhonen[1] | Mikael O. Ekblad[1]

[1]Department of General Practice, Institute of Clinical Medicine, University of Turku and Turku University Hospital, Turku, Finland

[2]KESSOTE Central Satakunta Health Federation of Municipalities, Harjavalta, Finland

[3]THL Finnish Institute for Health and Welfare, Helsinki, Finland

[4]Research Centre for Child Psychiatry, University of Turku, Turku, Finland

[5]Academic Primary Health Care Centre, Region Stockholm and Karolinska Institute, Stockholm, Sweden

Correspondence
Hanna P. Wallin, Department of General Practice, Institute of Clinical Medicine, University of Turku, Yleislääketiede, 20014 Turun yliopisto, Finland.
Email: hanna.p.wallin@utu.fi

Funding information
Suomalainen Lääkäriseura Duodecim; Duodecim; Research Foundation

Abstract

Introduction: Pregnancy itself predisposes to urinary tract infections (UTI). There appears to be a higher prevalence of infections and genitourinary diseases among pregnant smokers than among non-smokers. The present study is a retrospective observational register study aiming to investigate whether maternal smoking is associated with the prevalence of UTIs during pregnancy by utilizing a pregnancy-pair analysis.

Material and Methods: Information about pregnancies and maternal smoking was obtained from the Finnish Medical Birth Register. The study sample consisted of all singleton pregnancies ($n = 723\,433$) of women giving birth between January 2006 and December 2018 in Finland. Information on maternal smoking was collected in three categories: (1) non-smoking; (2) quit smoking during the first trimester; and (3) continued smoking throughout the pregnancy. Information about maternal UTI diagnoses during pregnancy was received from the Hospital Discharge Register and the Medical Birth Register. UTIs were categorized as lower and upper UTIs according to the International Statistical Classification of Diseases and Related Health Problems (ICD)–10 diagnosis codes. Risks were calculated as odds ratios (OR) by logistic regression with 95% confidence intervals (CI) further adjusted for maternal characteristics (aOR). Finally, pregnancy-pair analyses were performed: mothers who had changed smoking status (no smoking/any smoking) between consecutive pregnancies ($n = 27\,246$ pregnancy-pairs) were analyzed as one cluster and compared with non-smokers.

Results: Smokers had UTIs more often compared with the non-smokers. The association was even stronger among those who continued to smoke (aOR 1.60, 95% CI 1.51–1.70) than among those who smoked only during the first trimester (aOR 1.27, 95% CI 1.18–1.37) compared with non-smokers. In pregnancy-pair analysis, smoking was associated with upper UTIs during pregnancy (OR 1.49, 95% CI 1.05–2.12) compared with non-smokers, but after the adjustments this association was attenuated (aOR

Abbreviations: aOR, adjusted odds ratio; BMI, body mass index; CI, confidence interval; ICD, International Statistical Classification of Diseases and Related Health Problems; MSDP, maternal smoking during pregnancy; UTI, urinary tract infection.

1.27, 95% CI 0.88–1.82). No association in lower UTIs was observed in the pregnancy-pair design.

Conclusions: Maternal smoking was associated with a higher prevalence of UTIs during pregnancy in the standard comparison. The observed association was fully attenuated in the pregnancy-pair analysis, in which smoking was dichotomized. This study suggests that the association between maternal smoking during pregnancy and adverse maternal health effects might be more complex than previously thought.

KEYWORDS
nicotine, pregnancy, pyelonephritis, smoking, urinary tract infection

1 | INTRODUCTION

Smoking has a detrimental effect on almost every organ,[1] and pregnant smokers appear to be at higher risk for different infections compared with non-smokers.[2,3] The prevalence of non-respiratory infection symptoms during pregnancy has been shown to be higher among women who smoke than among non-smokers, according to self-reported data.[4] Our previous study showed that maternal smoking during pregnancy (MSDP) was associated with more hospital care due to genitourinary diseases during pregnancy.[5] According to a Danish study, pregnant smokers received more antibiotic treatment for urinary tract infections (UTIs) during pregnancy compared with non-smokers.[6] However, the prevalence of bacteriuria during pregnancy has not been linked with MSDP.[7] Among young non-pregnant women, smoking does not seem to be a risk factor for UTIs.[8]

Pregnancy itself predisposes to UTIs due to the attendant hormonal changes that cause bladder relaxation and (over)dilation. During pregnancy, the growing uterus can compress the ureters and increase vesicoureteral reflux, and the immune response is also compromised.[9] The known risk factors for UTI during pregnancy include prior UTIs, medically indigent status, diabetes (gestational or mellitus) and neurogenic bladder condition.[10]

The prevalence of asymptomatic bacteriuria during pregnancy is typically between 2% and 10%, with the prevalence of cystitis between 1% and 2%, and acute pyelonephritis – a more severe type of UTI – up to 1%.[11] Approximately one of every four pregnant women will present with a UTI if asymptomatic bacteriuria is untreated.[10] Pregnant women with asymptomatic bacteriuria during pregnancy seem to have a 20- to 30-fold risk of developing pyelonephritis during the later stages of pregnancy.[12] In general, maternal UTIs are associated with preeclampsia, especially during the third trimester of pregnancy.[13,14] Pyelonephritis also compromises the health of the fetus by increasing the risk for preterm birth.[15] Moreover, maternal complications include acute respiratory distress syndrome, septicemia and anemia.[16]

It is therefore essential to thoroughly investigate the potential association between MSDP and UTIs during pregnancy. Studies examining the effects of MSDP on child behavior have revealed that investigating the effects of smoking on different outcomes is not as straightforward as previously thought.[17] Thus, it has become necessary to use quasi-experimental designs to disentangle the effects of MSDP from other unmeasurable confounders.

Key message

Smoking was associated with a higher prevalence of urinary tract infections during pregnancy. This was not observed in the pregnancy-pair analysis, which might imply that the association between smoking and adverse maternal health effects might be more convoluted than formerly perceived.

The aim of this study was to investigate the association between MSDP and UTIs during pregnancy. We hypothesized that MSDP, especially when continued beyond the first trimester, would be associated with more UTIs during pregnancy compared with non-smoking. Furthermore, we used a pregnancy-pair design approach to examine the role of smoking in further detail in those mothers who had discordant smoking exposure in consecutive pregnancies.

2 | MATERIAL AND METHODS

2.1 | Data sources

The present work draws on a population-based register study that utilized data from the Finnish Medical Birth Register and the Hospital Discharge Register. The Finnish Medical Birth Register includes data regarding all live births, as well as stillbirths with birthweights over 500 g or from the gestational age of 22 weeks onwards. These data are received from the delivery hospitals or from the health personnel assisting in the rare home births. The register contains both mother's and child's identification numbers, information about maternal background, pregnancy, obstetric care and delivery. Maternal body mass index (BMI), infertility treatments and diagnoses during pregnancy

and delivery have been collected since 2004 and have been available from all delivery hospitals since 2006. The data are collected according to the International Statistical Classification of Diseases and Related Health Problems (ICD)–10 codes, which may include information from both primary healthcare providers and hospitals. According to data quality studies, the Medical Birth Register data correspond well or satisfactorily with hospital records.[18,19]

Since 1969, the Hospital Discharge Register has included information regarding all episodes of inpatient care at public and private hospitals; since 1998, it also includes information on outpatient visits to public hospitals. The register contains information on each patient's background, dates of admission and discharge, number of hospitalization days, procedures and main diagnosis (plus up to two other ICD-10 diagnoses since 1996). Outpatient visits mainly include physician visits but might also include nurse and midwife visits. A systematic review showed that the completeness and accuracy of the register ranges from satisfactory to very good.[20]

2.2 | Study sample

The study population consisted of all pregnant women who gave birth between January 2006 and December 2018 in Finland ($n = 744\,532$). Women with multiple pregnancies (twin/triplet pregnancies) ($n = 21\,099$, 2.8%) were excluded. Thus, the final study sample consisted of 723 433 pregnant women (97.2% of all births during the study period). Some women had more than one pregnancy during the study period, hence the study population consisted of 429 929 women. The data on MSDP were derived from the Medical Birth Register. Midwives and public health nurses collected information about MSDP in three categories, categorized according to the following three groups: (1) non-smoking women (82.5%); (2) women who quit smoking during the first trimester (5.7%); and (3) women who continued smoking throughout the pregnancy (8.8%). The information on smoking status was missing from the record for 21 800 singleton pregnancies (3.0%; see Table 1 for details). The register does not denote a distinction between women who have never smoked and women who might have recently quit smoking, nor does it contain information about exposure to secondhand smoke.

2.3 | UTI diagnoses

UTI diagnoses were acquired from the Hospital Discharge Register and linked with the data from the Medical Birth Register by the mothers' unique encrypted personal identification numbers. The diagnoses were analyzed according to the ICD-10 diagnosis codes. We included both the pregnancy-related UTI diagnoses (from the ICD-10 Chapter O) and the UTI diagnoses from the ICD-10 genitourinary chapter (Chapter N) to ensure full coverage of UTI diagnoses, as codes from both chapters might be used during pregnancy. These UTI diagnoses were then combined to form the analysis set (any UTI) and further divided into lower UTI and upper UTI groups. Lower UTIs consisted of diagnosis codes N30, N39.0, O23.1, O23.4, O23.9, N34 and O23.2; upper UTIs used codes N10, N11, N12 and O23.0 (see Table S1 for details). The participants were most likely diagnosed in primary-care facilities or prenatal clinics if this information was not found in the Hospital Discharge Register. The nonspecific symptom code R82.7 for abnormal findings in the microbiological examination of urine was left out of our analysis, as the number of such diagnoses was small and the inclusion of these cases would not have altered the results.

2.4 | Statistical analyses

First, the association between maternal smoking status and UTI diagnosis during pregnancy was analyzed using logistic regression analyses. Mothers who had more than one UTI diagnosis within the same category were considered only once. We accounted for the confounding factors as available, including year of delivery (to eliminate differences in diagnostics and any changes in the organization of maternal care), maternal age (continuous) and parity (0, 1–4, or 5 or more), and BMI (continuous) before pregnancy. We also analyzed the amount of outpatient and inpatient care (the number of episodes and the cumulative number of hospitalization days) according to the same UTI categories as noted above. This was done using independent sample *t*-tests, wherein *P*-values <0.05 were considered statistically significant.

Secondly, we conducted a pregnancy-pair analysis to examine the effect of smoking in further detail and to eliminate intrinsic maternal factors. The conditional logistic regression analysis was carried out for those women who had changed their smoking status in consecutive pregnancies, ie non-smoking to any smoking or, more often, vice versa. Different pregnancies of the same mother were grouped into a single cluster. Altogether, we found that 27 246 mothers had smoked during one consecutive pregnancy but not during the other. Please see Figure 1 flow chart for details. The smoking group was then compared with the non-smoking group. We accounted for the same confounding factors as previously mentioned. To test our pregnancy-pair design, we performed sensitivity analyses to examine the associations between MSDP and birthweight, which have been shown to be causally related. The sensitivity analysis replicated the causal association between MSDP and birthweight, which confirmed that there was indeed a difference in terms of the mother's smoking status.

The data analysis was performed using commercially available software (SAS, version 9.4, SAS Institute Inc., Cary, NC, USA). Non-overlapping confidence intervals were considered to be significant.

2.5 | Ethics statement

In Finland, ethical review is not required for register-based studies if the registered persons are not contacted. The Finnish Institute for Health and Welfare is the current maintainer of the registers that were utilized and allowed the use of the confidential health register data in scientific research as required by national data-protection legislation. The

TABLE 1 Characteristics of the study population

	No. of pregnancies	Maternal smoking		Any UTI	
		n	%	*n*	%
n	723433	104933	14.5%	9416	1.3%
Maternal age, years					
<20	14959	7139	47.7%	611	4.1%
20–34	566005	85423	15.1%	7537	1.3%
≥35	142469	12371	8.7%	1268	0.9%
Parity					
0	300326	52438	17.5%	4965	1.7%
1	244896	28805	11.8%	2513	1.0%
2 or 3	142516	19893	14.0%	1583	1.1%
≥4	35260	3786	10.7%	351	1.0%
Unknown	435	11	2.5%	4	0.9%
BMI					
<20	95510	15470	16.2%	1337	1.4%
20–24.9	364506	46101	12.6%	4364	1.2%
25–29.9	156397	24364	15.6%	2026	1.3%
30–34.9	59713	11108	18.6%	916	1.5%
≥35	30037	6250	20.8%	517	1.7%
Unknown	17270	1640	9.5%	256	1.5%
Marital status					
Married	299841	69186	23.1%	4754	1.6%
Cohabiting	411857	33218	8.1%	4426	1.1%
Single	8635	2081	24.1%	177	2.0%
Unknown	3100	448	14.5%	59	1.9%
SES					
Upper white-collar	103862	4519	4.4%	760	0.7%
Lower white-collar	211637	28502	13.5%	2285	1.1%
Blue-collar	79365	19889	25.1%	1125	1.4%
Other/unknown	328569	52023	15.8%	5246	1.6%

Abbreviations: BMI, body mass index; UTI, urinary tract infection.

statistical authority made the ethical evaluation and performed the data linkage, and only unidentifiable data were provided to the researchers.

3 | RESULTS

The prevalence of MSDP was 14.5% in the first trimester, and 8.8% of women continued to smoke throughout their pregnancies. The characteristics of the study population according to maternal smoking status are presented in Table 1. In total, 1.3% of women experienced a UTI during pregnancy.

3.1 | Diagnoses

Pregnant smokers had more often received a UTI diagnosis during pregnancy compared with non-smokers (Table 2). This association was even stronger if the mother had continued smoking (adjusted odds ratio [aOR] 1.60, 95% confidence interval [CI] 1.51–1.70) compared with those mothers who quit smoking in the first trimester (aOR 1.27, 95% CI 1.18–1.37). There was a similar finding in our separate analyses of upper UTI and lower UTI.

3.2 | Hospital treatment

Pregnant smokers who continued to smoke after the first trimester, had more inpatient care episodes for UTI ($p = 0.015$) compared with those who quit or did not smoke. No difference was found in the number of hospitalization days or in the number of outpatient visits between the groups (Table 3). Further, no difference between the groups was observed when hospital care was analyzed for lower UTI and upper UTI separately.

FIGURE 1 The pregnancy-pair design

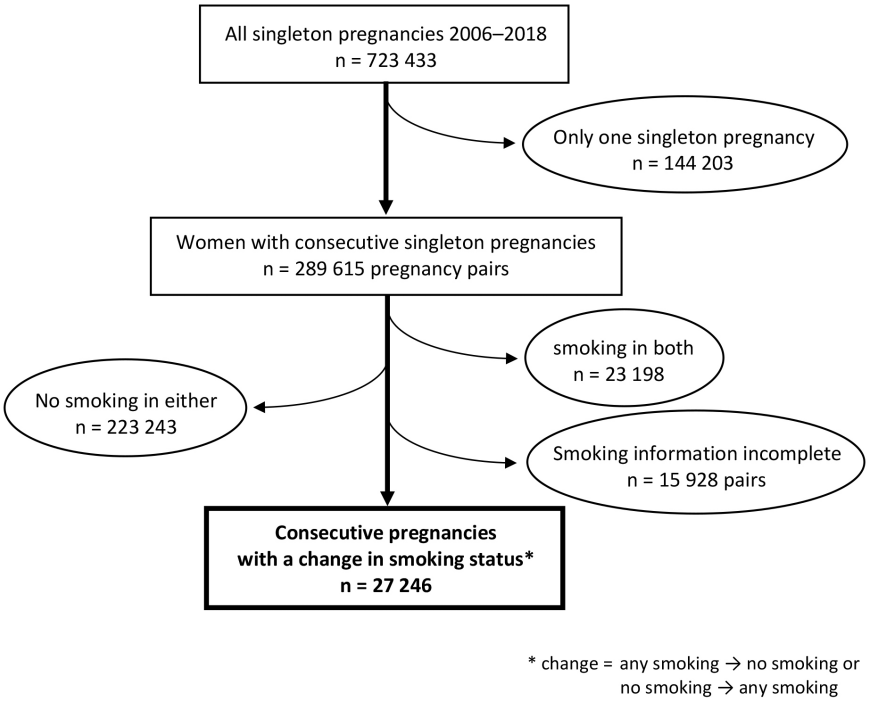

TABLE 2 Effect of maternal smoking during pregnancy on the prevalence of urinary tract infections during pregnancy

	No smoking	Quit smoking	Continued smoking	Missing smoking information	Total
n	596 700	41 404	63 529	21 800	723 433
Any UTI					
n	6902	786	1420	308	9416
Rate per 1000	11.6	19.0	22.4	14.1	13.0
Crude OR (95% CI)	1 (reference)	1.64 (1.52–1.77)	1.94 (1.83–2.05)		
Adjusted OR (95% CI)	1 (reference)	1.27 (1.18–1.37)	1.60 (1.51–1.70)		
Lower UTI					
n	5316	590	1020	226	7152
Rate per 1000	8.9	14.2	16.1	10.4	9.9
Crude OR (95% CI)	1 (reference)	1.60 (1.47–1.74)	1.81 (1.69–1.93)		
Adjusted OR (95% CI)	1 (reference)	1.25 (1.15–1.36)	1.55 (1.44–1.66)		
Upper UTI					
n	1461	185	401	63	2110
Rate per 1000	2.4	4.5	6.3	2.9	2.9
Crude OR (95% CI)	1 (reference)	1.82 (1.56–2.12)	2.57 (2.30–2.87)		
Adjusted OR (95% CI)	1 (reference)	1.34 (1.15–1.57)	1.85 (1.65–2.08)		

Note: Adjusted for maternal age, parity, prepregnancy BMI, year of delivery.
Abbreviations: CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

3.3 | Pregnancy-pair analysis

In our pregnancy-pair comparison, 69% of women who changed their smoking status, had smoked in the first of their consecutive pregnancies. We found that there was a statistically significant difference in the likelihood for upper UTIs, with an odds ratio (OR) of 1.49 (95% CI 1.05–2.12) among smokers compared with non-smokers. However, after adjusting for confounding factors, this association was fully attenuated (aOR 1.27, 95% CI 0.88–1.82). There was no difference between smokers and non-smokers in the likelihood for (any) UTI (aOR 1.16, 95% CI 0.96–1.40) or lower UTI (aOR 1.10, 95% CI 0.87–1.38) (see Table 4 for details).

TABLE 3 Hospital treatment due to different urinary tract infection diagnoses according to smoking status

		No smoking		Quit smoking			Continued smoking			Missing information on smoking		
		Episodes	Per 100 persons	Episodes	Per 100 persons	*p*	Episodes	Per 100 persons	*p*	Episodes	Per 100 persons	*p*
Any UTI	Inpatient care	1788	25.9	208	26.5	0.761	422	29.7	0.015	67	21.8	0.117
	Inpatient days	7906	114.5	845	107.5	0.518	1745	122.9	0.325	319	103.6	0.468
	Outpatient visits	6597	95.6	741	94.3	0.665	1376	96.9	0.625	293	95.1	0.934
Lower UTI	Inpatient care	1032	19.4	117	19.8	0.826	200	19.6	0.901	33	14.6	0.064
	Inpatient days	4604	86.6	474	80.3	0.622	829	81.3	0.567	160	70.8	0.289
	Outpatient visits	5530	104	595	100.8	0.321	1096	107.5	0.238	244	108	0.533
Upper UTI	Inpatient care	915	62.6	110	59.5	0.51	269	67.1	0.272	38	60.3	0.78
	Inpatient days	3993	273.3	445	240.5	0.139	1124	280.3	0.74	183	290.5	0.736
	Outpatient visits	1493	102.2	186	100.5	0.852	396	98.8	0.65	59	93.7	0.587

Abbreviation: UTI, urinary tract infection.

TABLE 4 Pregnancy-pair comparison for the association between maternal smoking and urinary tract infections during pregnancy

	Non-smoking	Smoking
n	27 246	27 246
Any UTI		
n	434	465
Rate per 1000	15.9	17.1
Crude OR (95% CI)	1 (reference)	1.19 (0.99–1.43)
Adjusted OR (95% CI)	1 (reference)	1.16 (0.96–1.40)
Lower UTI		
n	76	110
Rate per 1000	2.8	4.0
Crude OR (95% CI)	1 (reference)	1.10 (0.88–1.37)
Adjusted OR (95% CI)	1 (reference)	1.10 (0.87–1.38)
Upper UTI		
n	339	340
Rate per 1000	12.4	12.5
Crude OR (95% CI)	1 (reference)	1.49 (1.05–2.12)
Adjusted OR (95% CI)	1 (reference)	1.27 (0.88–1.82)

Note: Adjusted by maternal age, parity, prepregnancy BMI, year of delivery.

Abbreviations: CI, confidence interval; OR, odds ratio; UTI, urinary tract infection.

4 | DISCUSSION

To our knowledge, this is the first study to examine the association between MSDP and UTIs considering intrinsic maternal factors. In the standard comparison, MSDP was strongly associated with the prevalence of UTIs during pregnancy, as we had hypothesized.[5] This finding is in agreement with the few previous studies that showed more antibiotic treatment for UTIs and more self-reported genitourinary symptoms during pregnancy among smokers.[4,10] There was also a clear effect of the duration of smoking exposure, as those who continued to smoke throughout the pregnancy more often had UTI compared with those who quit during the first trimester.

Only a small number of studies have thoroughly investigated the effect of the amount and/or duration of MSDP on maternal health outcomes. Strong evidence points to increased risk of stillbirth, preterm birth, perinatal death and birth defects as the number of cigarettes smoked by the mother increases.[21] Previous studies have examined the effects of MSDP on UTIs using only a dichotomous categorization of MSDP.[4,10] In our study, we found that the duration of MSDP affected the risk of UTI, including the stronger association between MSDP and UTI. This was observed among mothers who continued to smoke during later pregnancy in comparison with mothers who quit smoking during the first trimester. Thus, quitting smoking even during the first trimester has beneficial effects on maternal health.

MSDP was also associated with more inpatient care due to a UTI of any level. The association in our study was even stronger regarding

upper UTIs, which are the more severe type of UTIs. Moreover, MSDP was only associated with an increased number of hospitalizations due to upper UTIs in the group who had continued smoking after the first trimester. This emphasizes that MSDP might increase the risk for more serious UTI that require hospital treatment. We found no difference in the length of hospitalization or in the number of outpatient visits between the smoking and non-smoking groups.

However, the observed association between MSDP and UTIs was fully attenuated in our pregnancy-pair design, which utilized information from women with discordant smoking status in consecutive pregnancies and hence allowed us to eliminate some unmeasurable maternal factors (eg genetic). In other words, mothers did not experience more UTIs during the pregnancies in which they smoked than during the pregnancies in which they did not smoke. It is more common for smoking mothers to smoke during their first pregnancy (69%) and then quit before the following pregnancy than for the opposite to be true.[22,23] Thus it is possible that smoking might have some longer lasting effects on the function of the mucous membranes, which may explain some predisposition to UTIs in later pregnancies.

Unfortunately, the pregnancy-pair analysis did not account for the duration of MSDP, as smoking was dichotomized as simply "no smoking" and "any smoking", where the latter included both mothers who quit smoking in the first trimester and those who continued smoking after that point. It is likely that not all maternal confounders could be eliminated, such as other lifestyle factors (eg substance use). The possibility that the simultaneous presence of other maternal factors might interact with MSDP and predispose a woman to UTIs exists.

The strengths of this study include the use of a large national study population accounting for all singleton pregnancies (97.2% of all births) from January 2006 to December 2018. This data included information from all of Finland through national registers, which have been shown to be reliable for research purposes.[18,20] Another strength of this study is that we obtained information on pregnant women who quit smoking during their first trimester, as well as those who continued smoking throughout their pregnancy; this allowed us to evaluate the effect of the duration of MSDP. This comprehensive data also enabled us to engage in more detailed analysis. Furthermore, to our knowledge, this is the first study to utilize this type of pregnancy-pair analysis.

One limitation of this data is the accuracy of the smoking information, which was based only on mothers' self-reported information and was collected by public health nurses and midwives in prenatal clinics. The reliability of the MSDP data of the Finnish Medical Birth Register has been found to be satisfactory,[18] but people tend to underestimate their level of smoking.[24] As a consequence, our results might underestimate the effects of MSDP. On the other hand, it seems that self-reporting is an appropriate source for epidemiological study purposes when analyzing dose correlation during pregnancy.[25] Unfortunately, information about maternal smoking before pregnancy is not collected, which leads to a "non-smoking" group that also includes women who stopped smoking before becoming pregnant. There is evidence that the effects of smoking on fertility and overall health are not immediately reversed upon smoking cessation.[26] The registers do not include information about a partner's smoking either, hence the effect of second-hand smoke exposure could not be studied.

In this study, we had access to data regarding diagnoses during pregnancies from both the Hospital Discharge Register, including diagnoses from specialized hospital care, and the Finnish Medical Birth Register, including up to 10 diagnoses made during pregnancy. Therefore, our data should include those lower UTIs that are mainly diagnosed at primary healthcare and maternity clinics. It seems that our study sample is quite representative, as 1.0% of women had lower UTI during pregnancy, which is in line with previous studies.[11] Despite the large sample size in our study, the number of UTIs remained relatively low, and thus more research should be conducted to study the causality of the relation between MDSP and UTIs.

In future, it will be important to obtain other reliable data from primary healthcare providers, where the majority of UTIs are treated. This could be done, for example, by utilizing information from the Drug Prescription Register. Access to mothers' medical histories could also offer valuable information for understanding the predisposition towards UTIs in pregnant women in further research.

5 | CONCLUSION

In this study, no association between MSDP and UTI during pregnancy could be confirmed, although there were robust findings in the standard model, especially regarding continued smoking and more severe upper UTIs. Pregnancy-pair analyses with women who changed their smoking habits between two or more consecutive pregnancies showed that the association found in the standard model was fully attenuated. This study proposes that the relation between MSDP and adverse maternal health effects might be more complex than expected.

AUTHOR CONTRIBUTIONS

HPW and PEK contributed to study design and manuscript writing. MG contributed to statistics design, data collection and analysis, and manuscript writing. MOE contributed to study and statistics design, as well as to manuscript writing.

FUNDING INFORMATION

The data permit charge was supported by the Duodecim Research Foundation.

CONFLICT OF INTEREST

None.

ORCID

Hanna P. Wallin https://orcid.org/0000-0001-9616-8956

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Wallin HP, Gissler M, Korhonen PE, Ekblad MO. New insights into smoking and urinary tract infections during pregnancy using pregnancy-pair design: A population-based register study. *Acta Obstet Gynecol Scand*. 2023;102:25-32. doi: 10.1111/aogs.14473