SUPPLEMENTARY APPENDIX

Husby et al. Pregnancy duration and endometrial cancer risk: nationwide cohort study

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Supplementary Methods

Coding of hospital diagnoses

Diagnosis	ICD-8 (1977-1994)	ICD-10 (1995-)
Obesity	'277.99'	'E66', 'E66.0', 'E66.2', 'E66.8', 'E66.9'
Endometriosis	'625.30', '625.31', '625.32', '625.33', '625.34', '625.35', '625.36', '625.37', '625.38', '625.39'	'N80', 'N80.0', 'N80.1', 'N80.2', 'N80.3', 'N80.4', 'N80.5', 'N80.6', 'N80.8', 'N80.9'
Endometrial hyperplasia	'625.20'	'N85.0', 'N85.1'
Polycystic ovarian syndrome and other ovarian dysfunction	'256.09', '256.19', '256.90', '256.99'	'E28', 'E28.0', 'E28.1', 'E28.2' , 'E28.3', 'E28.8', 'E28.9'
Spontaneous abortion	'64380', '64381', '64382', '64389', '64390', '64391', '64392', '64399'	'O03', 'O03.0', 'O03.1', 'O03.2', 'O03.3', 'O03.4', 'O03.5', 'O03.6', 'O03.7', 'O03.8', 'O03.9'.

Coding of surgical procedures

Surgical procedure	Danish Classification of Surgical Procedures and Therapies (1977-1995)	Nordic Medico-Statistical Committee Classification of Surgical Procedures (1996-)
Hysterectomy	'61000', '61020', '61040', '61050', '61100'	'KMCA33', 'KLCD00', 'KLCD01', 'KLCD04', 'KLCD10', 'KLCD11', 'KLCD30', 'KLCD31', 'KLCD40', 'KLCD96', 'KLCD97', 'KLEF13'
Bilateral oophorectomy	'60120', '60121', '60320'	'KLAE20', 'KLAE20A', 'KLAE21', 'KLAF10', 'KLAF10A', 'KLAF11'

Histological subtypes of endometrial cancer with corresponding ICD-O-3 codes

Events defined as endometrial cancer if ICD10 code was "C54-55" and ICD-O-3 code ended in "3".

Histological subtypes:

Type I endometrial cancer (6,203 events):

Endometrioid adenocarcinoma: 8380, 8381, 8382, 8383
Tubular adenocarcinoma: 8210, 8211
Papillary adenocarcinoma: 8260, 8262, 8263
Squamous adenocarcinoma: 8570
Mucinous adenocarcinoma: 8480, 8481
Adenocarcinoma NOS: 8140
Adenocarcinoma with squamous differentiation: 8560, 8570

Type II endometrial cancer (485 events):

Clear cell adenocarcinoma: 8310
Serous adenocarcinoma: 8441
Papillary serous adenocarcinoma: 8460, 8461
Squamous cell adenocarcinoma: 8050, 8070, 8071, 8072
Adenosquamous adenocarcinoma: 8560
Small cell carcinoma: 8041
Mixed cell adenocarcinoma: 8323

Minor histological subtypes (55 events):

Carcinoma NOS: 8010
Carcinoma, undifferentiated, NOS: 8020
Carcinoma, anaplastic, NOS: 8021
Small cell carcinoma, NOS: 8041
Verrucous carcinoma, NOS: 8051
Papillary squamous carcinoma, NOS: 8052
Squamous cell carcinoma, microinvasive: 8076
Basaloid squamous cell carcinoma: 8083
Superficial spreading adenocarcinoma: 8143
Adenoid cystic carcinoma: 8200
Solid carcinoma, NOS: 8230
Mucoepidermoid carcinoma: 8430
Cystadenocarcinoma, NOS: 8440
Papillary cystadenocarcinoma, NOS: 8450
Mucinous cystadenocarcinoma, NOS: 8470
Signet ring cell carcinoma: 8490
Adenocarcinoma with spindle cell metaplasia: 8572
Adenocarcinoma with apocrine metaplasia: 8573

Description of socioeconomic variables

Using nationwide registry information from the Danish Civil Registration System and Statistics Denmark on educational attainment, marital status, and place of residence we created a three-dimensional time-varying adjustment for socioeconomic status. The following categorization of the socioeconomic factors were used:

Educational attainment

Information on education was used to create a characterization of educational attainment grouped in the following groups; primary schooling, short basic education, higher education, and missing educational information(only 6.9% of person-years and 0.8% of events had missing information on educational attainment). Further description of educational attainment groups are given below:

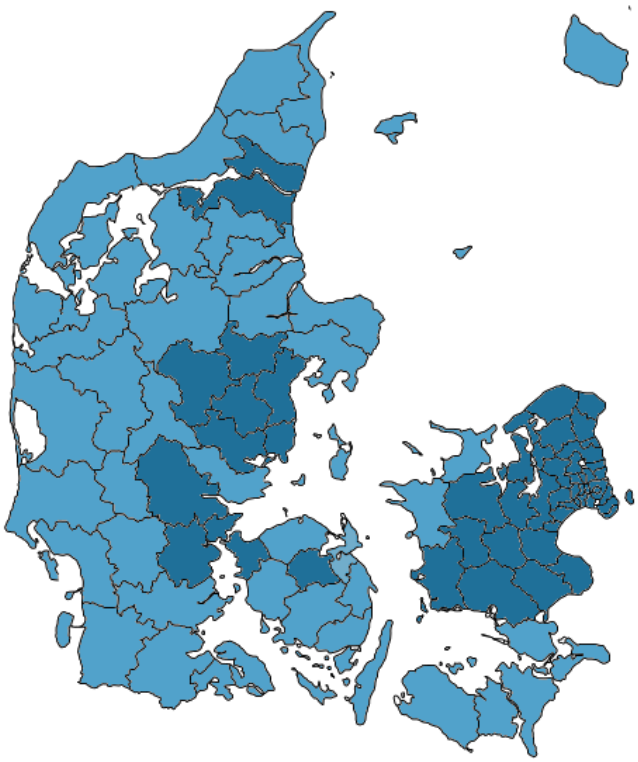
Educational attainment	Primary schooling	*Primary schooling*
	Short basic education	*High school with technical or mercantile focus; short basic education*
	Higher education	*High school; higher education of short duration; higher education of medium duration; academic bachelor degree; academic master's degree; higher education of long duration*
	Missing information	*No register information available*

Marital status

Marital status was categorized as either married, divorced, widowed or unmarried based on information from the Danish Civil Registration System.

Urbanicity

For characterization of urbanicity, Danish municipalities were categorized as either urban or rural based on an urbanization definition used by The Danish Ministry for Economic Affairs and the Interior(1). The definition is based on 14 indicator variables, such as population per square kilometre, percentage of population employed in agricultural enterprises, and average distance to motorway (see nationwide map of urban and rural municipalities below).



Map of municipalities by urbanicity status: **Dark blue** denoting urban municipalities and **light blue** denoting rural municipalities.

Figure S1. Relative risk of endometrial cancer following a pregnancy (both induced abortions and childbirths) compared with one pregnancy less stratified by first and any subsequent pregnancy and by A) age at pregnancy and B) time since pregnancy. Estimates are adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and age, educational attainment, marital status, and urbanicity, respectively.

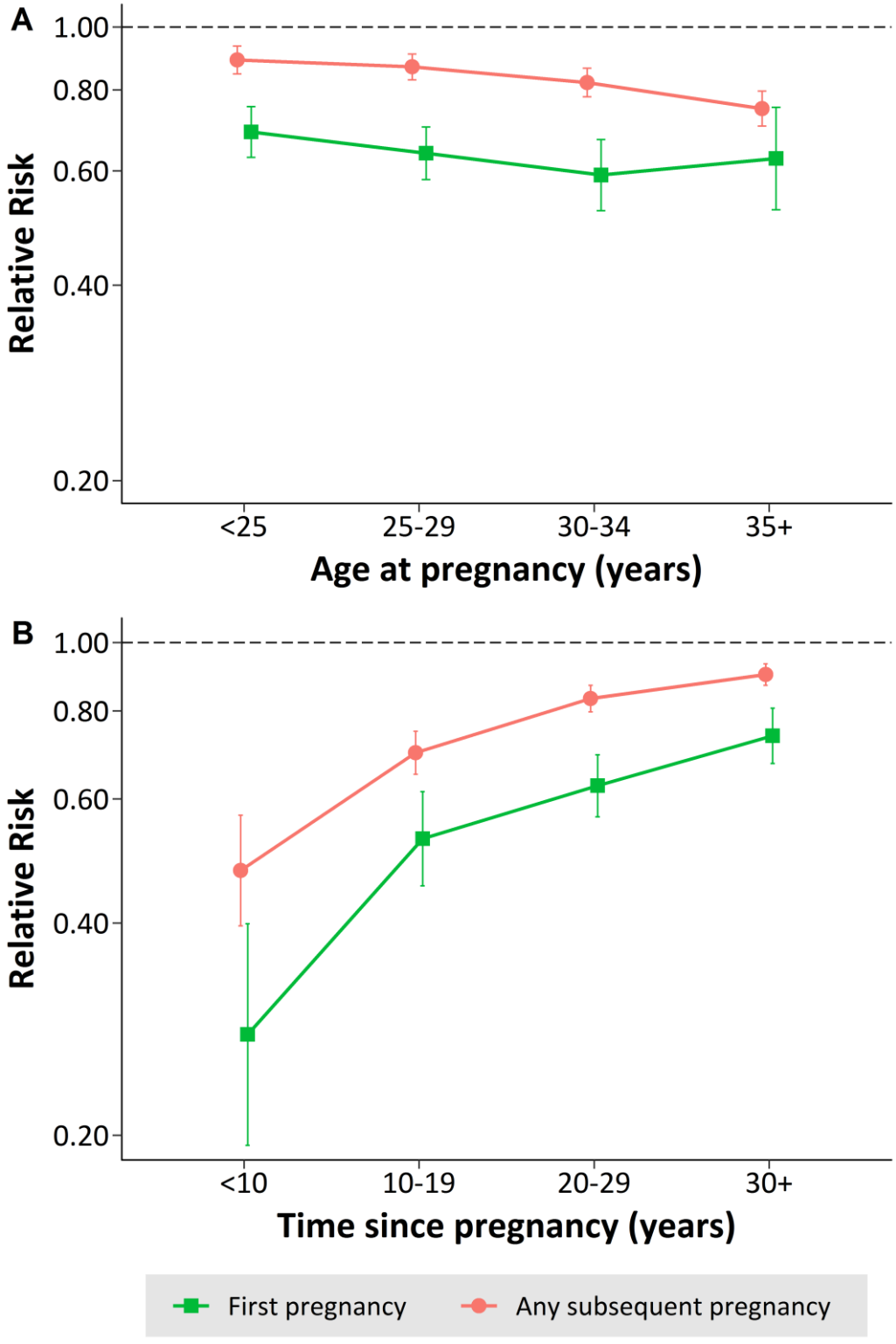


Figure S2. Timeline of important historical events in Denmark with regards to the study period.

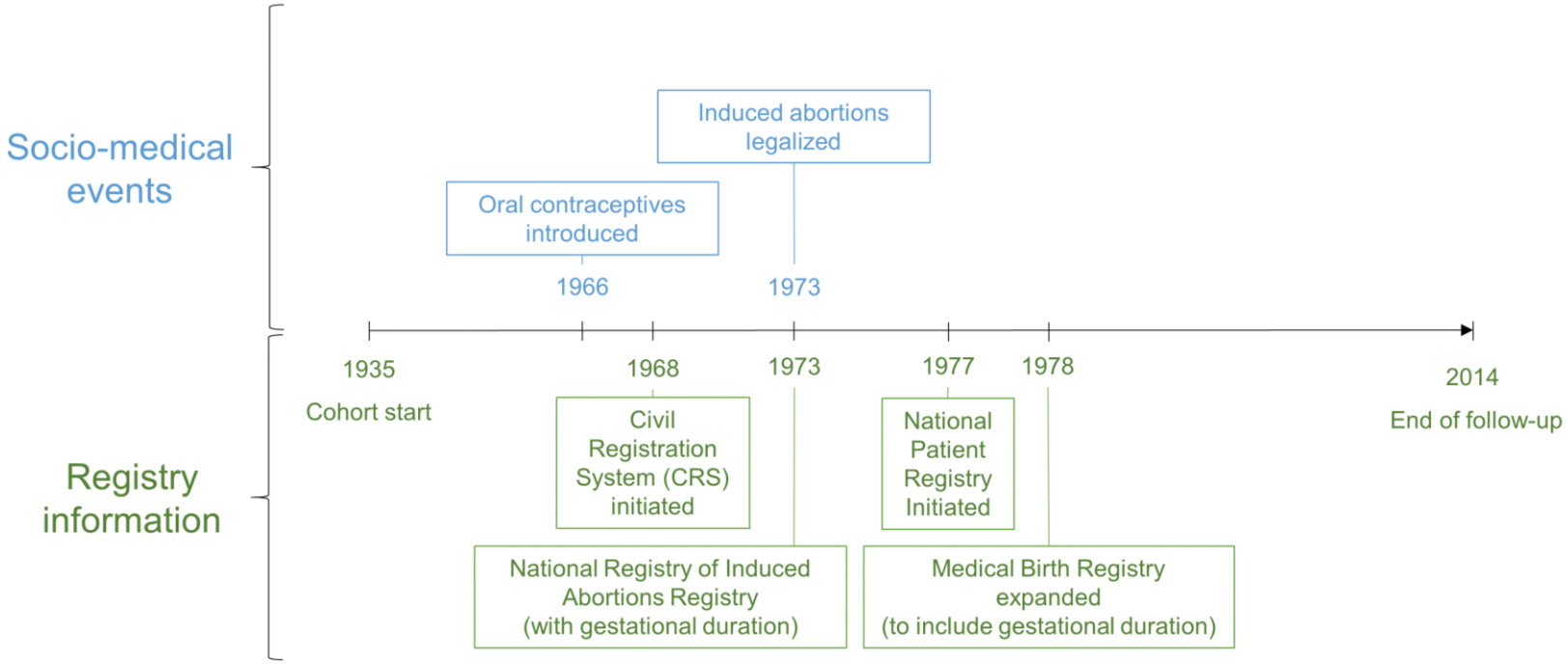


Table S1. Description of study cohort. Person-years and endometrial cancer events are shown according to number of induced abortions, number of childbirths, age at first childbirth, time since last childbirth, birth cohort, educational attainment, marital status, and urbanicity based on follow-up from January 1978 to December 2014.

Characteristic	Person-years (in 1000s) (%)		Endometrial cancer events (%)	
Total cohort	57348	(100.0 %)	6743	(100.0 %)
Number of induced abortions				
0	47520	(82.9 %)	5871	(87.1 %)
1	7371	(12.9 %)	710	(10.5 %)
≥ 2	2457	(4.3 %)	162	(2.4 %)
Number of childbirths				
0	23018	(40.1 %)	1078	(16.0 %)
1	8597	(15.0 %)	1161	(17.2 %)
2	17069	(29.8 %)	2904	(43.1 %)
3	6679	(11.6 %)	1207	(17.9 %)
≥ 4	1985	(3.5 %)	393	(5.8 %)
Age at first pregnancy (years)				
< 30	32745	(90.3 %)	5215	(91.2 %)
≥ 30	3509	(9.7 %)	502	(8.8 %)
Age at latest pregnancy (years)				
< 30	41882	(73.0 %)	4281	(63.5 %)
≥ 30	15466	(27.0 %)	2462	(36.5 %)
Duration of latest pregnancy (weeks)				
Nulligravid women	21094	(36.8 %)	1026	(15.2 %)
< 12	6269	(10.9 %)	698	(10.4 %)
12-21	139	(0.2 %)	15	(0.2 %)
22-36	894	(1.6 %)	64	(0.9 %)
≥ 37	16008	(27.9 %)	1001	(14.8 %)
Missing gestational duration	12944	(22.6 %)	3939	(58.4 %)
Time since latest pregnancy (years)				
< 10	37907	(66.1 %)	1149	(17.0 %)
≥ 10	19440	(33.9 %)	5594	(83.0 %)
Attained age at diagnosis (years)				
< 50	46157	(80.5 %)	929	(13.8 %)
≥ 50	11191	(19.5 %)	5814	(86.2 %)
Birth cohort				
1935-1939	3974	(6.9 %)	1852	(27.5 %)
1940-1944	5057	(8.8 %)	1812	(26.9 %)
1945-1949	6163	(10.7 %)	1547	(22.9 %)
1950-1959	11917	(20.8 %)	1229	(18.2 %)
1960-	30236	(52.7 %)	303	(4.5 %)
Educational attainment				
Primary schooling	21365.9	(37.3 %)	2875	(42.6 %)
Short basic education	16367.3	(28.5 %)	2213	(32.8 %)
Higher education	15637.6	(27.3 %)	1600	(23.7 %)
Missing information	3976.9	(6.9 %)	55	(0.8 %)
Marital status				
Married	25754	(44.9 %)	4496	(66.7 %)
Divorced	4664	(8.1 %)	826	(12.2 %)

Widowed	1235	(2.2 %)	718	(10.6 %)
Unmarried	25695	(44.8 %)	703	(10.4 %)
Urbanicity				
Rural	21560	(37.6 %)	2822	(41.9 %)
Urban	35787	(62.4 %)	3921	(58.1 %)

Table S2. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less by pregnancy number and type, for all pregnancies and for pregnancies from 1973.

		Adj. relative risk of endometrial cancer (95% CI)*	
Pregnancy number	**Pregnancy type**	**All pregnancies recorded**	**Pregnancies from 1973†**
First pregnancy	Induced abortion	0.53 (0.45 to 0.64)	0.53 (0.44 to 0.63)
	Childbirth	0.66 (0.61 to 0.72)	0.57 (0.52 to 0.63)
Any subsequent	Induced abortion	0.81 (0.77 to 0.86)	0.81 (0.77 to 0.86)
	Childbirth	0.86 (0.84 to 0.89)	0.78 (0.74 to 0.81)

* Adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and age, educational attainment, marital status, and urbanicity, respectively.

† Same modelling as for all pregnancies recorded, but with estimates subdivided by whether they represent a pregnancy before or from 1973. Therefore, estimates for any subsequent pregnancy from 1973 are adjusted for any childbirths occurring prior to 1973.

Table S3. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less by pregnancy number and type, by adjustment for non-malignant endometrial and ovarian disease (endometriosis, endometrial hyperplasia, PCOS and other ovarian dysfunction*).

		Adj. relative risk of endometrial cancer (95% CI)† by adjustment	
Pregnancy number	**Pregnancy type**	**Non-adjusted estimates**	**Adjusted estimates**
First pregnancy	Induced abortion	0.53 (0.45 to 0.64)	0.54 (0.45 to 0.64)
	Childbirth	0.66 (0.61 to 0.72)	0.66 (0.61 to 0.72)
Any subsequent	Induced abortion	0.81 (0.77 to 0.86)	0.82 (0.77 to 0.87)
	Childbirth	0.86 (0.84 to 0.89)	0.86 (0.84 to 0.89)

* For definition of endometriosis, endometrial hyperplasia, PCOS and other ovarian dysfunction, see Supplementary methods.
† Adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and age, educational attainment, marital status, and urbanicity, respectively.

Table S4. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less by pregnancy number and type, by degree of socioeconomic adjustment.*

		Relative risk of endometrial cancer (95% CI)†, by socioeconomic adjustment				
Pregn. number	**Pregn. type**	**no SES-adj.**	**only education**	**only marital status**	**only urbanicity**	**all SES-factors**
First pregnancy	Ind. abortion	0.52 (0.44 to 0.62)	0.52 (0.44 to 0.62)	0.53 (0.44 to 0.63)	0.53 (0.45 to 0.63)	0.53 (0.45 to 0.64)
	Childbirth	0.66 (0.61 to 0.71)	0.66 (0.61 to 0.71)	0.66 (0.61 to 0.72)	0.66 (0.61 to 0.71)	0.66 (0.61 to 0.72)
Any subsequent	Ind. abortion	0.80 (0.76 to 0.85)	0.80 (0.76 to 0.85)	0.81 (0.77 to 0.86)	0.81 (0.76 to 0.86)	0.81 (0.77 to 0.86)
	Childbirth	0.88 (0.85 to 0.90)	0.87 (0.85 to 0.90)	0.87 (0.85 to 0.90)	0.87 (0.84 to 0.90)	0.86 (0.84 to 0.89)

* For further classification of socioeconomic variables see Supplementary Methods. For person-years and events with missing information on socioeconomic variables see Table S1.

† All estimates are adjusted for age, period, and interaction between period and age.

Table S5. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less by pregnancy number and pregnancy type, among women with and without a diagnostic hospital code for obesity.*

		Relative risk of endometrial cancer (95% CI)	
		Among women with an obesity diagnosis* events = 522, person-years = 815,456	
Pregnancy number	**Pregnancy type**	**Non-adjusted estimates†**	**Adjusted estimates‡**
First pregnancy	Induced abortion	0.53 (0.31 to 0.91)	0.57 (0.34 to 0.98)
	Childbirth	0.54 (0.42 to 0.70)	0.58 (0.44 to 0.77)
Any subsequent	Induced abortion	0.79 (0.65 to 0.96)	0.81 (0.66 to 0.99)
	Childbirth	0.88 (0.80 to 0.96)	0.87 (0.79 to 0.96)
		Among women without an obesity diagnosis* events = 6221, person-years = 56,532,166	
Pregnancy number	**Pregnancy type**	**Non-adjusted estimates†**	**Adjusted estimates‡**
First pregnancy	Induced abortion	0.53 (0.44 to 0.64)	0.54 (0.45 to 0.65)
	Childbirth	0.68 (0.63 to 0.74)	0.67 (0.62 to 0.73)
Any subsequent	Induced abortion	0.80 (0.76 to 0.85)	0.82 (0.76 to 0.87)
	Childbirth	0.87 (0.84 to 0.89)	0.85 (0.83 to 0.88)

* The sub-cohort of clinically obese women were followed from date of the obesity diagnosis, giving 815,456 person-years and 522 events. Using information on body mass index (BMI) from the Medical Birth Registry, we found that among the women who had a registered BMI measurement, mean BMI was measured to 32.2 kg/m^2 in the obesity sub-cohort, as opposed to a mean BMI of 23.6 kg/m^2 among those not in the obesity sub-cohort. Furthermore, we found that the mean BMI in the obesity sub-cohort was 33.6 kg/m^2 for women with 10 years or more between clinical diagnosis of obesity and BMI measurement.

† Adjusted only for age, period, and interaction between period and age.

‡ Adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and age, educational attainment, marital status, and urbanicity, respectively.

Table S6. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less by pregnancy number and type, stratified by birth cohort.

		Adj. relative risk of endometrial cancer (95% CI)*, stratified by birth cohort				
Pregn. number	**Pregn. type**	**1935-1939**	**1940-1944**	**1945-1949**	**1950-1959**	**1960-**
First pregnancy	Ind. abortion	0.64 (0.27 to 1.56)	0.58 (0.31 to 1.10)	0.42 (0.25 to 0.70)	0.58 (0.44 to 0.76)	0.38 (0.24 to 0.59)
	Childbirth	0.71 (0.60 to 0.83)	0.68 (0.57 to 0.81)	0.72 (0.60 to 0.87)	0.66 (0.56 to 0.79)	0.32 (0.23 to 0.44)
Any subsequent	Ind. abortion	0.82 (0.70 to 0.97)	0.80 (0.71 to 0.90)	0.82 (0.74 to 0.92)	0.82 (0.73 to 0.92)	0.86 (0.68 to 1.09)
	Childbirth	0.88 (0.84 to 0.93)	0.89 (0.84 to 0.94)	0.84 (0.78 to 0.90)	0.79 (0.73 to 0.86)	0.83 (0.70 to 0.98)

* Adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and age, educational attainment, marital status, and urbanicity, respectively.

Table S7. Relative risk of endometrial cancer following a pregnancy compared to having one pregnancy less by pregnancy number and pregnancy type, including spontaneous abortions.*		
Pregnancy number	**Pregnancy type**	**Adj. relative risk of endometrial cancer (95% CI)†**
First pregnancy	Induced abortion	0.54 (0.44 to 0.66)
	Spontaneous abortion‡	0.80 (0.62 to 1.03)
	Childbirth	0.53 (0.47 to 0.59)
Any subsequent	Induced abortion	0.79 (0.74 to 0.85)
	Spontaneous abortion‡	0.91 (0.81 to 1.04)
	Childbirth	0.75 (0.71 to 0.79)

* Effect of pregnancies from 1977, when registration of spontaneous abortions began, while adjusting for any previous pregnancies.

† Adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and respectively age, educational attainment, marital status, and urbanicity.

‡ There were 189,111 registered spontaneous abortions for women in the cohort.

Table S8. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less among women with at least three pregnancies who had either less than five years between their first and third pregnancy (termed the high fecundity sub-cohort), or more (termed the non-high fecundity sub-cohort).*

Pregnancy number	**Sub-cohort**	**Adj. relative risk of endometrial cancer (95% CI)**†
Fourth or more	High fecundity sub-cohort	0.86 (0.80 to 0.92)
	Non-high fecundity sub-cohort	0.88 (0.80 to 0.97)

* The sub-cohort of high fecundity women were followed from the date of their third pregnancy, giving 11,206,608 person-years and 1824 events. Women with three pregnancy or more not in the high fecundity sub-cohort were also followed from their third pregnancy, which gave 2,843,773 person-years and 424 events.

† Adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and age, educational attainment, marital status, and urbanicity, respectively.

Table S9. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less by pregnancy number and pregnancy type, with start of follow-up from 20 years of age.		
Pregnancy number	**Pregnancy type**	**Adj. relative risk of endometrial cancer (95% CI)***
First pregnancy	Induced abortion	0.53 (0.45 to 0.64)
	Childbirth	0.66 (0.61 to 0.72)
Any subsequent	Induced abortion	0.81 (0.77 to 0.86)
	Childbirth	0.86 (0.84 to 0.89)

* Adjusted for age, period, educational attainment, marital status, urbanicity, and interaction between period and age, educational attainment, marital status, and urbanicity, respectively.

Table S10. Relative risk of endometrial cancer following a pregnancy compared with having one pregnancy less by pregnancy number and type, by cancer stage from 2010 following revision of FIGO guidelines for staging of endometrial cancer.*

		Adj. relative risk of endometrial cancer (95% CI)† by *cancer stage‡*	
Pregnancy number	**Pregnancy type**	**Stage I** events = 1500	**Stage II-IV** events = 459
First pregnancy	Induced abortion	0.49 (0.36 to 0.66)	0.67 (0.40 to 1.11)
	Childbirth	0.60 (0.51 to 0.72)	0.59 (0.43 to 0.80)
Any subsequent	Induced abortion	0.82 (0.73 to 0.92)	0.78 (0.63 to 0.96)
	Childbirth	0.90 (0.84 to 0.96)	0.94 (0.84 to 1.06)

* Analyses by competing risks between stage groups and other cancers.

† Adjusted for age, educational attainment, marital status, and urbanicity.

‡ Analysis of cancer stage included 9,184,686 person-years and was based on follow-up time from 2010. Missing stage and low stage was grouped together.

Supplementary Appendix References

1. Ministry of Food, Agriculture and Fisheries The European Agricultural Fund for Rural Development 2 Contents [Internet]. 2012 [cited 2018 Sep 20]. Available from: https://naturerhverv.dk/fileadmin/user_upload/NaturErhverv/Filer/Tilskud/Projekttilskud/Landdistrikter/LDP_Rev_proposal_Consolid_2007-2013f.pdf