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Use of antidepressants and association with elective termination of pregnancy: population based case–control study

H Kieler,[a] H Malm,[b,c] M Artama,[d] A Engeland,[e,f] K Furu,[e] M Gissler,[g,h] M Nørgaard,[i] O Stephansson,[a,j] U Valdimarsdottir,[k,l] H Zoega,[k] B Haglund[a]

[a] Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden [b] Teratology Information Service, HUSLAB and Helsinki University Central Hospital, Helsinki, Finland [c] Department of Clinical Pharmacology, [d] Department of Medical Genetics, Helsinki University, Helsinki, Finland [e] Division of Epidemiology, Department of Pharmacoepidemiology, Norwegian Institute of Public Health, Oslo, [f] Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway [g] Nordic School of Public Health, Gothenburg, Sweden [h] THL National Institute for Health and Welfare, Helsinki, Finland [i] Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark [j] Division of Obstetrics and Gynecology, Department of Women's and Children's Health, Karolinska Institutet, Stockholm, Sweden [k] Centre of Public Health Sciences, School of Health Sciences, University of Iceland, Reykjavik, Iceland [l] Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA
Correspondence: Dr H Kieler, Centre for Pharmacoepidemiology, Karolinska Institutet, Building T2, Karolinska University Hospital, SE 171 76 Stockholm, Sweden. Email helle.kieler@ki.se

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Objective To assess whether the use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, mirtazapine, venlafaxine or other antidepressants is associated with late elective termination of pregnancy.

Design Case–control study using data from national registers.

Setting Denmark, Finland, and Norway during the period 1996–2007.

Population A total of 14 902 women were included as cases and 148 929 women were included as controls.

Methods Cases were women with elective termination of pregnancy at 12–23 weeks of gestation. Controls continued their pregnancy and were matched with cases on key factors.

Main outcome measures Association between antidepressant use during pregnancy and elective termination of pregnancy at 12–23 weeks of gestation for fetal anomalies, or for maternal ill health or socio-economic disadvantage.

Results At least one prescription of antidepressants was filled by 3.7% of the cases and 2.2% of the controls. Use of any type of antidepressant was associated with elective termination of pregnancy for maternal ill health or socio-economic disadvantage (odds ratio, OR 2.3; 95% confidence interval, 95% CI 2.0–2.5). Elective termination of pregnancy for fetal anomalies was associated with the use of mirtazapine (OR 2.2, 95% CI 1.1–4.5). There was no association between the use of any of the other antidepressants and elective termination of pregnancy for fetal anomalies.

Conclusion The use of any type of antidepressants was associated with elective termination of pregnancy at 12–23 weeks for maternal ill health or socio-economic disadvantage, but not with terminations for fetal anomalies. Further studies need to confirm the findings concerning mirtazapine and termination of pregnancy for fetal anomalies.

Keywords Antidepressants, fetal anomaly, socio-economic disadvantage, termination of pregnancy.

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Introduction

Around 10% of pregnant women meet the criteria for major depression and about 20% show high depression scale scores, indicative of depressive symptomatology.[1,2] Selective serotonin-reuptake inhibitors (SSRIs) are the most frequently used antidepressants during pregnancy, and their use is increasing.[3,4] Some studies have reported increased risks for congenital anomalies in association with the use of SSRIs or tricyclic antidepressants.[5–14] Risks of adverse birth outcomes in association with other antidepressants are largely unknown.[15–17] Most of the studies that reported

associations between antidepressants and anomalies included data on liveborn infants only, or did not explicitly address elective termination of pregnancy (TOP). Risks of congenital anomalies in association with drug use might be underestimated if TOP is not taken into consideration. On the other hand, women on antidepressants may terminate their pregnancy because of fear concerning teratogenic effects.[18]

To assess the association between the use of antidepressants and TOP we conducted a multinational case–control study including women with a TOP at 12–23 weeks of gestation as cases, and women who continued their pregnancies further than their matched case as controls. We studied associations between use of any antidepressant and TOP, and by type of antidepressant (SSRIs, tricyclic antidepressants, mirtazapine, venlafaxine, and other antidepressants). To elucidate the reasons for TOP we performed stratified analyses and assessed associations with TOP because of fetal anomalies, or because of maternal ill health or socio-economic disadvantage.

Methods

Using a case–control study design, we selected as cases women with a TOP at 12–23 weeks of gestation. Controls were matched with cases by country of residence, calendar year of pregnancy end point, age, and parity. The controls were selected among all women who had a TOP at a later stage than their matched case or who subsequently gave birth.

The women were residents in Denmark, Finland, and Norway, and ended their pregnancies between 1996 and 2007. All three countries have national registers that include prospectively collected health and social information on all residents. The registers include the Civil Personal Registration (CPR) numbers, a unique number assigned to each resident at birth or immigration. Reporting to the registers is mandatory and regulated by national laws. The national parliaments have, on behalf of their populations, given informed consent to be included in the registers.[19] We obtained data from the birth and termination of pregnancy registers, the patient registers, and the prescription registers.

The national health registers

Data on pregnancy and maternal demographics are included in the birth and termination of pregnancy registers, and/or the patient registers in Denmark, Finland, and Norway.[20] All liveborn births and all stillbirths after 22 weeks of gestation are recorded in the registers. In Norway, individual data are only obtained for women with TOP for a major risk that the fetus may suffer from a severe disorder or for risks of harmful influences to the woman during pregnancy.[21] In Denmark and Finland information on all terminations is recorded, together with the reasons for TOP.[22] In the registers the diagnoses and pregnancy complications are classified according to the national version of the International Classification of Diseases (ICD), and for the period of study ICD-10 was used. Gestational age, as recorded in the registers, was primarily based on the first day of the last menstrual period (LMP), as estimated by prenatal ultrasound. The prescription registers include data on dispensed item, substance, brand name, and formulation, together with date of dispensing for over 95% of the total outpatient population. All drugs are classified according to the World Health Organization Anatomical Therapeutic Chemical (ATC) classification. In general, prescriptions are filled for a maximum of 3 months.[23]

Case definition, control selection, and data collection

All women who terminated their pregnancies 84–167 days after LMP and recorded in the registers were eligible as cases. For each case we randomly selected ten controls using risk-set sampling. The cases had terminated their pregnancies between 1 January 1996 and 31 December 2007, and the controls had a continuing pregnancy at the corresponding gestational age. The controls could be matched with more than one case. Only pregnancies from the years in which prescription data were available, and when the ICD-10 coding was used in the registers, were included. Accordingly, the years included were: Denmark 1997–2007, Finland 1996–2006, and Norway 2005–2007 (Table 1). From the registers we obtained information on age, time of the TOP or delivery, indication for TOP, parity, number of previous terminations (early or late), and filled prescriptions of antidepressants, antidiabetics, antiepileptics, and other teratogenic drugs, such as agents acting on the renin–angiotensin system and antineoplastic agents. Information on antineoplastic agents could not be obtained from Denmark. Among the cases, we identified those who had filled prescriptions with any of these drugs from 90 days prior to LMP until the TOP. Analogous information was obtained for the controls.

Exposure variables

The antidepressants used during the study period were predefined and the following were included in the analyses: SSRIs (fluoxetine, citalopram, paroxetine, sertraline, fluvoxamine, and escitalopram), tricyclic antidepressants (imipramine, klomipramine, trimipramine, amitriptylin, nortriptyline, doxepine, dosulepine, amoxapine, and maproteline), mirtazapine, venlafaxine, and 'other' antidepressants (moklobemide, mianserine, trazodone, nefazodone, bupropion, milnacipran, reboxetine, and duloxetine).

Exposure was defined as one or more filled prescriptions from 90 days before LMP until 7 days before the TOP for the index case.

Statistical analyses

We used conditional logistic regression analysis to estimate associations between antidepressant use during pregnancy and TOP. For each gestational age among the cases, controls were matched with cases by country of residence, age, and parity. The women selected as controls could either have had a TOP at a later gestational week than the case that they were matched with or had given birth. Comparisons were made between cases and controls concerning exposure to any antidepressant and by type of antidepressant. The controls followed the case strata that they were matched with, throughout the analyses. Type of antidepressant was grouped as: (1) SSRI; (2) tricyclic antidepressants; (3) mirtazapine; (4) venlafaxine; or (5) other antidepressants.

The analyses were performed using two models: one including the matching variables (model 1) and the other additionally adjusting for use of antidiabetics, antiepileptics, or other teratogenic drugs (model 2). Women with missing data were excluded from the multivariate analysis. For women exposed to only one type of antidepressant during the exposure period, the odds ratios (ORs) are presented together with 95% confidence intervals (95% CIs) in Tables 2 and 3. In addition, 99% CIs were computed. We analysed associations between use of any antidepressant and TOP by type of antidepressant, and in stratified analyses by the reason for the TOP, i.e. fetal anomalies, or maternal ill health or socio-economic disadvantage. For exposure to any antidepressant we further explored whether a history of previous TOP or whether young age (i.e. below 20 years of age) influenced the associations with TOP. Lastly, the effect of narrowing the exposure period from 90 days before to 30 days before LMP was evaluated.

All analyses were conducted using SAS 9.3 (SAS Institute Inc., Cary, NC, USA). The study was approved (no. 2008/1371-31/4) by the Regional Ethical Review Board at Karolinska Institutet in Stockholm, Sweden, the National Board of Health, Denmark, the Danish Data Protection Agency, the National Institute for Health and Welfare of Finland, Statistics Finland, and the Norwegian Data Inspectorate.

Results

A total of 14 902 women with TOP were included as cases and 148 929 women were included as controls. Characteristics of the women included are presented in Table 1. The mean age was 28.1 years and of the 163 831 women, 30 340 (18.5%) were younger than 20 years of age. Previous TOP was more common among cases than among controls (19.8 versus 0.2%). Among the cases, 13 231 (88.8%) had a TOP before 20 weeks of gestation. The reason for TOP was recorded for 94.8%: 40% had a TOP for fetal anomalies, and 60% had a TOP for maternal ill health or socio-economic disadvantage. At least one prescription of antidepressants was filled by 550 (3.7%) of the cases, as compared with 3275 (2.2%) of the controls. SSRIs were the most commonly used antidepressants, both among cases (71.3%) and controls (76.8%).

Exposure to any antidepressant was associated with TOP (OR 1.7, 95% CI 1.6–1.9; Table 2). An association was found in all drug groups, although the associations with tricyclic antidepressants and with other antidepressants were imprecise. The highest OR was in association with exposure to venlafaxine (OR 3.3, 95% CI 2.3–4.7). All risk estimates were unchanged or slightly attenuated when adjusting for exposure to antidiabetics, antiepileptics, or other teratogenic drugs (model 2).

In the stratified analyses by reason for TOP we observed no association with the use of any antidepressants or specifically with SSRIs and TOP for fetal anomalies (Table 3). Few women had been exposed to the other antidepressant drug groups. Women exposed to mirtazapine had a doubled OR of TOP because of fetal anomaly (OR 2.2, 95% CI 1.1–4.5, 99% CI 0.9–5.7). Any antidepressant use more than doubled the OR of TOP for maternal ill health or socio-economic disadvantage (OR 1.8–5.1).

Stratifying for one or more previous terminations yielded almost identical risk estimates among women with a previous TOP and among women without a previous TOP. For women with no previous termination the OR of TOP for fetal anomaly by antidepressant use was 1.0 (95% CI 0.9–1.3), and for women with previous TOP the OR was 1.0 (95% CI 0.4–2.8). When considering TOP because of maternal ill health or socio-economic disadvantage, women with no previous TOP had an OR of 1.9 (95% CI 1.6–2.1), by antidepressant use. The corresponding OR among women with previous TOP was 2.0 (95% CI 1.1–3.5).

Exposure to any antidepressants below 20 years of age yielded an OR for a TOP, irrespective of reason, of 0.7 (95% CI 0.5–1.0). The corresponding OR for women aged 20 years or older was 1.9 (95% CI 1.7–2.1). Setting the start of the exposure period to 30 days before LMP had only minor influence on the risk estimates (OR 1.7, 95% CI 1.6–1.9). Excluding neoplastic agents from the definition of other teratogenic drugs in an analysis restricted to Finland and Norway, the countries where such information could be obtained, did not influence the risk estimates.

Discussion

Main findings

In this register-based study assessing associations between TOP at 12–23 weeks of gestation and exposure to antide-

Table 1. Maternal characteristics

Characteristics	No. (%) of cases (*n* = 14 902)	No. (%) of controls (*n* = 148 929)	Total no. (%) (*n* = 163 831)
Country of residence (years of inclusion)			
Denmark (1997–2007)	6567 (44.1)	65 588 (44.0)	72 155 (44.0)
Finland (1996–2006)	7747 (52.0)	77 461 (52.0)	85 208 (52.0)
Norway (2005–2007)	588 (3.9)	5880 (3.9)	6468 (3.9)
Maternal age (years)			
≤24	5532 (37.1)	55 311 (37.1)	60 843 (37.1)
25–34	5755 (38.6)	57 547 (38.6)	63 302 (38.6)
35–44	3543 (23.8)	35 428 (23.8)	38 971 (23.8)
≥45	72 (0.5)	643 (0.4)	715 (0.4)
Parity			
1	8802 (59.1)	87 940 (59.0)	96 742 (59.0)
2 or 3	4960 (33.3)	49 599 (33.3)	54 559 (33.3)
≥4	1140 (7.6)	11 390 (7.6)	12 530 (7.6)
Previous termination of pregnancy			
0	11 946 (80.2)	148 633 (99.8)	160 579 (98.0)
1	2127 (14.3)	232 (0.2)	2359 (1.4)
≥2	829 (5.6)	64 (0.0)	893 (0.5)
Maternal use of antidepressants*			
No	14 352 (96.3)	145 654 (97.8)	160 006 (97.7)
Yes	550 (3.7)	3275 (2.2)	3825 (2.3)
Maternal use of drugs for diabetes**			
No	14 765 (99.1)	148 087 (99.4)	162 852 (99.4)
Yes	137 (0.9)	842 (0.6)	979 (0.6)
Maternal use of drugs for epilepsy***			
No	14 737 (98.9)	148 091 (99.4)	162 828 (99.4)
Yes	165 (1.1)	838 (0.6)	1003 (0.6)
Maternal use of other teratogenic drugs******			
No	14 855 (99.7)	148 728 (99.9)	163 583 (99.8)
Yes	47 (0.3)	201 (0.1)	248 (0.2)

*ATC-code N06A, **ATC-code A10, ***ATC-code N03A, ****agents acting on the renin-angiotensin system and antineoplastic agents (ATC-codes C09, L01, or L04).

Table 2. Exposure to antidepressants and odds ratios for termination of pregnancy by type of drug

Type of drug	No. of women exposed to antidepressants (per 1000)		Odds ratio (95% CI)	
	Cases	Controls	Model 1*	Model 2**
Any antidepressant	550 (36.9)	3275 (22.0)	1.7 (1.6–1.9)	1.7 (1.5–1.8)
SSRI***	392 (26.3)	2515 (16.9)	1.6 (1.4–1.8)	1.6 (1.4–1.7)
Tricycllic antidepressant	23 (1.5)	174 (1.2)	1.3 (0.9–2.1)	1.3 (0.8–1.9)
Mirtazapine	34 (2.3)	130 (0.9)	2.7 (1.8–3.9)	2.6 (1.8–3.9)
Venlafaxine	38 (2.5)	119 (0.8)	3.3 (2.3–4.7)	3.0 (2.1–4.3)
Other antidepressants****	15 (1.0)	95 (0.6)	1.6 (0.9–2.8)	1.5 (0.9–2.7)

*Adjusted by conditioning for gestational age in weeks, country of residence, year, maternal age and parity.
**Adjusted by conditioning, as in model 1, and for use of antidiabetics, antiepileptics, or other teratogenic drugs (ATC-codes C09, L01, or L04).
***Selective serotonin reuptake inhibitor.
****Moklobemide, mianserin, trazodone, nefazodone, bupropion, milnacipran, reboxetine, or duloxetine.

Table 3. Exposure to antidepressants and odds ratio for termination of pregnancy by type of drug and reason for termination

Reason for termination of pregnancy	Drug class	No. of women exposed to antidepressants (per 1000)		Odds ratio (95% CI)	
		Cases	Controls	Model 1*	Model 2**
Fetal anomaly	Any antidepressant	134 (23.7)	2341 (21.7)	1.1 (0.9–1.3)	1.0 (0.9–1.3)
	SSRI***	95 (16.8)	1792 (16.6)	1.0 (0.8–1.2)	1.0 (0.8–1.2)
	Tricyclic antidepressant	8 (1.4)	129 (1.2)	1.0 (0.5–2.1)	1.0 (0.5–2.0)
	Mirtazapine****	9 (1.6)	83 (0.8)	2.2 (1.1–4.5)	2.2 (1.1–4.5)
	Venlafaxine	6 (1.1)	92 (0.9)	1.2 (0.5–2.7)	1.2 (0.5–2.7)
	Other antidepressants*****	6 (1.1)	66 (0.6)	1.6 (0.7–3.8)	1.6 (0.7–3.7)
Maternal ill health or socio-economic disadvantage	Any antidepressant	395 (46.6)	2674 (21.5)	2.3 (2.0–2.5)	2.2 (2.0–2.5)
	SSRI***	286 (33.8)	2078 (16.7)	2.1 (1.8–2.4)	2.0 (1.8–2.3)
	Tricyclic antidepressant	13 (1.5)	131 (1.1)	1.8 (1.0–3.2)	1.7 (0.9–3.0)
	Mirtazapine	25 (3.0)	111 (0.9)	3.1 (2.0–4.8)	3.1 (2.0–4.7)
	Venlafaxine	29 (3.4)	96 (0.8)	5.1 (3.4–7.9)	4.6 (3.0–7.1)
	Other antidepressants*****	8 (0.9)	69 (0.6)	1.9 (0.9–3.9)	1.8 (0.8–3.7)

*Adjusted by conditioning for gestational age in weeks, country of residence, year, maternal age, and parity.
**Adjusted by conditioning, as in model 1, and for use of antidiabetics, antiepileptics, or other teratogenic drugs (ATC-codes C09, L01, or L04).
***Selective serotonin reuptake inhibitor.
****99% CI included 1.0.
*****Moklobemide, mianserin, trazodone, nefazodone, bupropion, milnacipran, reboxetine, or duloxetine.

pressants, we found associations with SSRIs, with mirtazapine, and with venlafaxine. Most importantly the positive associations were mainly apparent when the reason for TOP was maternal ill health or socio-economic disadvantage.

Strengths and limitations

Major strengths of the study include its multinational and population-based design, and the assessment of covariates such as young age and previous TOP. We used a case–control design and included as cases all women who had a TOP after gestational week 12 in three Nordic countries during the study period. Information on exposure to antidepressants and characteristics was prospectively collected, excluding the common validity concerns related to case–control studies because of recall bias. The design allowed us to match for important factors such as country of residency, year of pregnancy, age, and parity, and to take into consideration gestational week when terminating the pregnancy. The controls had either given birth to a child or terminated their pregnancy at a later stage than the cases. Previous studies assessing TOP have been criticised for comparisons with women who have given birth, as the ideal comparator should be any pregnant woman.[22] It is, however, unlikely that not including women with spontaneous abortions should have influenced the associated risks, as late spontaneous abortions occur in <2% of all pregnancies.[24]

Ultrasound scanning has been part of the standard antenatal care in the Nordic countries for several decades, and the ability to detect fetal anomalies by ultrasound has increased over the years.[25,26] In Denmark and Norway a woman may terminate her pregnancy before 13 weeks of gestation upon request; in Finland, a legal indication is required for early TOP.[22] In each country, later TOP is also possible for reasons of fetal anomaly, maternal ill health, and social or ethical circumstances, provided that permission from a national/regional decision-making committee is granted. Despite the clear distinction between early and late TOP in legal terms, one should acknowledge the uncertainty of estimation of gestational age, even by ultrasound scanning. In a study from Finland, with overlapping data from the present study, TOP for fetal reasons were slightly more common among SSRI users;[14] however, that study did not assess other reasons for TOP, and included both early and late terminations. Women on SSRIs might terminate their pregnancies for other reasons than fetal anomaly, such as fear of teratogenic effects of the drug, and therefore it is important to study other reasons for TOP as well. Also, as in this study, preferably only the later terminated pregnancies should be evaluated, as in contrast to early TOP they are most likely to be performed after an ultrasound examination, thereby verifying the suspicion of a fetal anomaly.

We did not have information on the reason for treatment or details of treatment. Hence it is possible that residual confounding by these unmeasured factors affected our risk estimates. Although information on dispensed drugs is not the same as intake of drugs, Nordic studies

showed good agreement of maternal antidepressant use, when comparing information on dispensed drugs with reported drug intake.[27,28] Exposure to more than one antidepressant was not assessed, but considering the short periods for evaluating exposure switching of antidepressants or add-on therapy should not be a major concern. The reasons for TOP could only be assessed for residents in Denmark and Finland, which, nonetheless, constituted more than 96% of the study population.

Interpretation

With a few exceptions, studies on the use of SSRIs and congenital anomalies have been based only on pregnancies resulting in the birth of a live child.[5–13] If a pregnancy is terminated for severe anomalies caused by a drug, and associations between the drug and the anomalies are based on live births only, such associations would yield underestimated risk estimates.

We found a doubled OR for TOP in association with maternal use of antidepressants. The association was only apparent in women aged 20 years or older, so pregnant teenagers terminating their pregnancies seem to do so independently of the use of antidepressants, which was also the case for women with a previous TOP. The majority of the women exposed to antidepressants had used SSRIs, and the OR associated with the use of an SSRI was in line with the use of any antidepressant.

In the analyses, where we stratified for reasons of TOP, the association seemed mainly to be driven by the association found for the use of antidepressants in women with ill health or socio-economic disadvantage. In particular, there was no association between TOP because of fetal anomalies and SSRI use, whereas the OR was increased two-fold for mirtazapine. It should be noted that for all of the drug groups the ORs were around twice as high for TOP because of ill health or socio-economic disadvantage than the estimates for TOP for fetal anomalies. As the association between TOP for fetal anomalies and use of mirtazapine was not statistically significant when applying the stricter level of significance (99% CI), this finding should be interpreted cautiously and evaluated further.[17]

The SSRIs are the most commonly used antidepressants during pregnancy, and our findings do not indicate an association between the use of SSRIs and TOP for fetal anomalies. Furthermore, we speculate that the mere use of antidepressants may cause concern about an adverse pregnancy outcome and make the pregnant woman and her doctor choose to terminate the pregnancy. An alternative explanation to our findings of an association between TOP for maternal reasons and use of antidepressants could be related to depression or depression-related symptoms despite medication, or other chronic diseases. Such an explanation is less likely as difficulties in managing the disease generally should be preceded by a change in treatment, such as a switching of antidepressant, which rarely happens during pregnancy.[4,29] Also, adjusting for the use of drugs considered to be teratogenic and used to treat other chronic conditions, such as diabetes, epilepsy, and other autoimmune diseases, had only minor effects on the ORs.

Conclusion

We found associations between late TOP and the use of antidepressants, such as SSRIs, venlafaxine, and mirtazapine. In women using SSRIs, the association was only apparent in women with a TOP for maternal ill health or socio-economic disadvantage. Conversely, the use of mirtazapine may be associated with termination for fetal anomalies. As SSRIs were not associated with elective termination for fetal anomalies, women treated with these drugs and their doctors should feel less stressed out about fetal outcomes. Further studies assessing associations between the newer antidepressants and congenital anomalies, such as mirtazapine, are warranted.

Disclosure of interests

All authors have completed the Unified Competing Interest form at www.icmje.org/downloads/coi_disclosure.pdf (available on request from the corresponding author), and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Contribution to authorship

HK is the guarantor and takes responsibility for the integrity of the data and the accuracy of the data analysis. HK, KF, MG, MN, UV, and BH were responsible for the conception and design of the study. MA, AE, MN, UN, and BH were responsible for the acquisition of data in their respective countries. HK drafted the article, obtained funding, and supervised the study. BH was responsible for the statistical analysis. All authors participated in the interpretation of data and critical revision of the article.

Details of ethics approval

The study was approved (no. 2008/1371-31/4): by the Regional Ethical Review Board at Karolinska Institutet in Stockholm, Sweden; the Danish Data Protection Agency and the National Board of Health, Denmark; the National Institute for Health and Welfare (THL), the Social Insurance Institution of Finland and Statistics Finland, Finland; the National Bioethics Committee and the Data Protection Authority in Iceland; and the Norwegian Data Inspectorate, Norway.

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