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ORIGINAL RESEARCH ARTICLE

Use of sildenafil and other phosphodiesterase type 5 inhibitors among pregnant women in Scandinavia

Carolyn E. Cesta[1] | Silvia Segovia Chacón[1] | Anders Engeland[2,3] | Anne Broe[4] | Per Damkier[4,5] | Kari Furu[3,6] | Helle Kieler[1,7] | Pär Karlsson[1]

[1]Department of Medicine Solna, Center for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden

[2]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway

[3]Department of Chronic Diseases and Ageing, Norwegian Institute of Public Health, Oslo, Norway

[4]Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Odense, Denmark

[5]Department of Clinical Research, University of Southern Denmark, Odense, Denmark

[6]Center for Fertility and Health, Norwegian Institute of Public Health, Oslo, Norway

[7]Department of Laboratory Medicine, Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden

Correspondence
Carolyn E. Cesta, Eugeniahemmet T2, Department of Medicine Solna, Karolinska Institutet, 171 76 Stockholm, Sweden.
Email: carolyn.cesta@ki.se

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Abstract

Introduction: For phosphodiesterase type 5 (PDE5) inhibitors, such as sildenafil, the only approved indication in women is for pulmonary arterial hypertension. These drugs are increasingly being proposed and tested for treatment of female infertility and complications in pregnancy. However, the extent of use of PDE5 inhibitors in the general pregnant population over the last decades is unknown. Therefore, we conducted a descriptive cohort study using data from the population health registers in the Scandinavian countries.

Material and methods: By linking the Medical Birth Registers and the Prescribed Drug Registers in Denmark (1997–2017), Norway (2004–2017), and Sweden (2006–2016), women with filled prescriptions of PDE5 inhibitors in outpatient settings in the 90 days before the date of last menstrual period and/or during pregnancies were identified. With additional linkage to the National Patient Registers, information on maternal, pregnancy, and infant characteristics, co-morbidities, and co-medication was collected and described.

Results: Among over 3 million singleton pregnancies, only 77 were pregnancies in women who had at least one filled prescription of a PDE5 inhibitor within the 90 days before the start of pregnancy to delivery. Prescription fills most often occurred before the last menstrual period and in the first trimester, with very few occurring later in pregnancy. Sildenafil was the most used PDE5 inhibitor. Among pregnant women using PDE5 inhibitors, 44% were 35 years of age or older, eight had a cardiovascular diagnosis, and three specifically had a diagnosis of pulmonary arterial hypertension. Among the infants born to mothers using PDE5 inhibitors, nine were born preterm, six were small-for-gestational age, five had an Apgar score at 5 minutes below 8, 18 were admitted to the Neonatal Intensive Care Unit, and eight had respiratory and cardiovascular conditions.

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; ICD, International Statistical Classification of Diseases and Related Health Problems; LMP, last menstrual period; MBR, Medical Birth Register; PAH, pulmonary arterial hypertension; PDE5, phosphodiesterase type 5; STRIDER trial, Sildenafil Therapy in Dismal Prognosis Early-Onset Fetal Growth Restriction.

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Conclusions: Few women used PDE5 inhibitors in outpatient settings before or during pregnancy in the Scandinavian countries in the last decades. Only a small proportion had a diagnosis for pulmonary arterial hypertension, suggesting off-label use in the remaining users. Use was predominantly in mothers over age 35 years. The safety of fetal exposure to sildenafil and other PDE5 inhibitors in pregnancy has not been established. As maternal age continues to increase and additional uses of PDE5 inhibitors are investigated, the safety of these drugs in pregnancy should be thoroughly evaluated.

KEYWORDS
drug utilization, pharmacoepidemiology, phosphodiesterase type 5 inhibitors, pregnancy, sildenafil

1 | INTRODUCTION

Phosphodiesterase type 5 (PDE5) inhibitors, specifically sildenafil, are most commonly known in perinatal research for the Sildenafil Therapy in Dismal Prognosis Early-Onset Fetal Growth Restriction (STRIDER) trials, the Dutch arm of which was halted in 2018, which aimed to test sildenafil as a treatment for fetal growth restriction.[1] However, in the past decade, clinical studies have also been initiated to test the effectiveness of sildenafil for treatment of female infertility,[2–5] for reducing intrapartum fetal distress,[6] and for the treatment of pre-eclampsia.[7] Further, sildenafil and other PDE5 inhibitors for the treatment of fetal growth restriction continues to be of interest to the research and clinical community[8,9] and continues to be investigated in clinical trials.[10] There is also interest in the therapeutic potential of PDE5 inhibitors for other chronic conditions including hypertension and diabetes.[11]

The safety profile of sildenafil was considered good with no evidence of harm in the limited number of pregnancy studies with available safety data before 2018. However, the Dutch arm of the STRIDER trials, which was published in 2019, reported increased risks of neonatal pulmonary hypertension.[1,9] Accordingly, there are concerns of the safety of these medications for exposed fetuses.[9,12–14] However, little is known about the use of PDE5 inhibitors in the general pregnant population.

In women, the only approved indication in Scandinavia for PDE5 inhibitors is pulmonary arterial hypertension (PAH).[11] PAH is more common in women than men, but overall prevalence is very low. Therefore, use of PDE5 inhibitors in pregnancy and the resulting fetal exposure in a real-world setting should be rare. A study based on data from the Sentinel Distributed Database in the USA from 2001 to 2018, reported a low prevalence of PDE5 inhibitor use among commercially insured pregnant women, with use in only 2.85 per 100 000 live-birth pregnancies; however, they report evidence of off-label use.[15]

The aim of this study was to investigate the use of PDE5 inhibitors before and during pregnancy in outpatient settings and to describe the maternal and infant characteristics of exposed pregnancies using population-based register data from Denmark, Norway, and Sweden.

Key Message

From 1997 to 2017 in the Scandinavian countries, use of phosphodiesterase type 5 inhibitors in pregnant women in outpatient settings was rare. However, as their use is increasingly being tested for conditions affecting reproductive-aged and pregnant women, their safety should be investigated.

2 | MATERIAL AND METHODS

We conducted an observational, population register-based cohort study that included women and their infants born in Denmark, Norway, and Sweden between 1997 and 2017. Each Nordic country has national registers, which include prospectively collected health information on all inhabitants. All data are linked via a unique personal identity number assigned to each resident at birth or immigration, which allows for accurate linkage of the individual-level data from different registers. Reporting to the registers is mandatory and regulated by national laws. From all three countries, we obtained data from the Medical Birth Registers (MBR), Prescribed Drug Registers, and Cause of Death Registers. From Denmark and Sweden, we also included data from the National Patient Registers. Data were analyzed separately in each country.

2.1 | Study population and study period

We identified all singleton pregnancies with deliveries after gestational week 22 between January 1, 1997 and December 31, 2017 in Denmark; January 1, 2005 and December 31, 2017 in Norway; and January 1, 2006 and December 31, 2016 in Sweden.

2.2 | Ascertainment of exposure

Filled prescriptions of PDE5 inhibitors from 90 days before the date of the last menstrual period (LMP) to the end of pregnancy were

identified in the Prescribed Drug Registers by Anatomical Therapeutic Chemical Classification System (ATC) code G04BE, including sildenafil (G04BE03), tadalafil (G04BE08), vardenafil (G04BE09), and avanafil (G04BE10). The Prescribed Drugs Registers do not include information on medications administered in inpatient settings. Five periods of exposure to PDE5 inhibitors were defined by at least one filled prescription in: (a) 90 days before LMP to the day before LMP, (b) first trimester (T1; defined as LMP to 98 days of gestation), (c) second trimester (T2; 99 to 196 days), (d) third trimester (T3; 197 to delivery), and (e) only in T2 or T3. Determination of LMP and gestational age was primarily based on prenatal ultrasound.

2.3 | Ascertainment of maternal characteristics

We described maternal pregnancy and delivery characteristics (Table 1), including information on: maternal age in years at delivery, parity, smoking in early pregnancy, and route of delivery. Maternal conditions were identified from diagnoses in the MBRs (Norway and Sweden) and diagnoses recorded in the year before LMP in the National Patient Registers (Denmark and Sweden). International Statistical Classification of Diseases and Related Health Problems version 10 (ICD-10) codes were used to identify: cardiovascular diagnoses overall (I00–I99), primary pulmonary hypertension/pulmonary arterial hypertension (I27), pre-eclampsia (O14 and O11.9), and gestational hypertension (O13.9). From the Prescribed Drug Registers, maternal co-medications were identified by at least one filled prescription from 90 days before LMP to the end of pregnancy of: cardiovascular system drugs (ATC C01-10), endocrine drugs (L02), immunosuppressants (L04), antihistamines (R06), and antivirals (J05A). These co-medications were selected based on the indication for PDE5 inhibitor use or on the drug classes considered to be contraindicated for sildenafil therapy at some sites of the STRIDER trials.[16]

Evidence for the reason of PDE5 inhibitor use (either on- or off-label) in the study population was explored by examining the reimbursement codes in the Prescribed Drug Registers in Norway and Denmark, and in Sweden by examining the prescribing physician's free text and co-medications and diagnoses in the 90 days before LMP to the end of the first trimester. Specifically, we looked for evidence of infertility and infertility treatment, Raynaud syndrome, and sexual dysfunction.

2.4 | Ascertainment of infant characteristics

We described infant characteristics (Table 2) including information on year of birth, gestational age at birth, sex, birthweight, Apgar score, and infant morbidity and mortality. Infants with a low Apgar score (<8) at 5 minutes after birth were identified. Small for gestational age (SGA) and large for gestational age were defined as a birthweight below or above 2 standard deviations of sex-specific and gestational-week-specific distributions, using country-specific reference standards.[17] Infant morbidity included recorded hospitalizations in the neonatal intensive care unit on the day of delivery, any recorded ICD-10 diagnoses of respiratory and cardiovascular disorders (P20–29), and specific recorded disorders including bronchopulmonary dysplasia (P27.1), respiratory distress syndrome

TABLE 1 Maternal characteristics of pregnancies exposed to PDE5 inhibitors

	Any PDE5 inhibitor	
	n	%
Total	77	
PDE5 inhibitors exposure by trimester		
90 days before LMP to LMP	39	51
First trimester	36	47
Second trimester	13	17
Third trimester	8	12
Only second or third trimester	13	17
Maternal age (years)		
≤24	5	8
25–29	14	23
30–35	24	39
≥35	34	44
Parity		
Primiparous	35	46
Multiparous	42	55
Smoking in early pregnancy		
Yes	9	12
No	63	82
Missing	4	5
Route of delivery		
Cesarean section	23	30
Vaginal delivery	54	70
Maternal cardiovascular-related diagnoses		
Cardiovascular diagnosis (ICD-10 I00–I99)	4	8
Pulmonary arterial hypertension (ICD-10 I27)	3	4
Pre-eclampsia (ICD-10 O14, O11.9)	0	
Gestational hypertension (ICD-10 O13.9)	($n < 3$)[a]	
Maternal co-medication in pregnancy[b]	54	70
Cardiovascular drugs (ATC C01–C10)	16	21
Endocrine drugs (ATC L02)	7	9
Immunosuppressants (ATC L04)	3	4
Antihistamines (ATC R06)	7	9
Antivirals (ATC J05A)	3	4

Abbreviations: ATC, Anatomical Therapeutic Chemical Classification System; ICD-10, International Statistical Classification of Diseases and Related Health Problems 10th revision; LMP, last menstrual period; PDE5 phosphodiesterase type 5.

[a]Numbers below 3 are reported as <3.

[b]Included filled prescriptions of medication from ATC chapters C, G, J, L, N, P and R, from 90 days before LMP until delivery.

TABLE 2 Characteristics of infants with prenatal exposure to PDE5 inhibitors

	Any PDE5 inhibitor	
	n	**Prevalence per 100 000[a]**
Total	77	2.3
Year of birth[b]		
1995–2000	4	1.5
2001–2005	11	2.9
2006–2010	27	2.3
2011–2015	28	2.5
2016–2017	7	2.0
Characteristic	***n***	**%**
Gestational age at birth		
Preterm (<37 weeks)	9	12
Term (37–41 weeks)	65	84
Post-term (≥42 weeks)	3	4
Sex		
Female	44	57
Male	33	43
Birthweight		
Low birthweight (<1500 g)	($n < 3$)[c]	
Moderate low birthweight (1500–2499 g)	6	9
Normal birthweight (2500–4499 g)	68	88
High birthweight (≥4500 g)	($n < 3$)[c]	
Birthweight categories[d]		
Small for gestational age	6	8
Average for gestational age	69	90
Large for gestational age	($n < 3$)[c]	
Apgar score at 5 min		
<8	5	7
Missing	($n < 3$)[c]	
Infant morbidity		
Hospitalization at NICU	18	23
Respiratory and cardiovascular disorders (ICD-10 P20–29)	8	10
Bronchopulmonary dysplasia (ICD-10 P27.1)	($n < 3$)[c]	
Respiratory distress syndrome (ICD-10 P22)	5	7
Aspiration syndromes (ICD-10 P24)	0	
Persistent fetal circulation (ICD-10 P29.3)	($n < 3$)[c]	
Infant mortality[e]		
Stillbirth	($n < 3$)[c]	
Neonatal death	0	
Post-neonatal death	($n < 3$)[c]	

Abbreviations: ICD-10, International Statistical Classification of Diseases and Related Health Problems version 10; PDE5 phosphodiesterase type 5.

[a]Calculated using the official statistics on number of births for each country for the years included in the study period.

[b]Data provided by Denmark for 1997 to 2017, Norway for 2005 to 2017, and Sweden for 2006 to 2016.

[c]Numbers below three are reported as <3.

[d]Small for gestational age and large for gestational age defined as birthweight below or above 2 standard deviations of sex- and gestational-week-specific distributions, using country-specific reference standard (Marsal et al., 1996).

[e]Stillbirth: >22 weeks of gestation. Neonatal death: 0–27 days. Post-neonatal death: 28–364 days.

(P22), neonatal aspiration syndrome (P24), and persistent fetal circulation (P29.3). Infant mortality data were collected from the MBRs and included information on stillbirth (defined as no evidence of life at birth after 22 weeks of gestation), neonatal death (defined as the death of a live-born infant within 0–27 days) and post-neonatal death (defined as death between 28 and 364 days after birth, identified in the cause of death registers). In the Danish MBR before 2004 and in the Swedish MBR before 2008, stillbirths were included after 28 weeks of gestation.

2.5 | Statistical analyses

The distribution of maternal and infant characteristics was described, by exposure to any PDE5 inhibitor drug, by presenting numbers and percentages. National statistics on the number of infants born in each contributing country per year were used to calculate the prevalence of PDE5 inhibitor exposure per 100 000 births for five birth-year categories. Statistics Denmark does not allow tabulation of numbers below 3, therefore we adopted this reporting strategy for all countries.

2.6 | Ethical approval

This study was approved by the Danish Health Data Authority (19/36067) on September 13, 2019, the Regional Committee for Medical and Health Research Ethics (REC-South East) and the Norwegian Data Inspectorate (REC-South East 2017/2546 on May 25, 2018), and the Stockholm Regional Ethical Review Board (Dnr 2015/1826-31/2 on November 18, 2015, 2017/2238-32, 2018/1790-32, 2018/2211-32). In all three countries, register-based studies are exempt from informed consent.

3 | RESULTS

From a total of 3 204 965 singleton pregnancies resulting in live birth from all three countries, 77 pregnancies (2.4 per 100 000) were in women who had at least one filled prescription of a PDE5 inhibitor within the 90 days before LMP to the end of pregnancy, of which 34 were from Denmark (years 1997–2017), 30 from Norway (2005–2017), and 13 from Sweden (2006–2016). The proportion of women using PDE5 inhibitors just before or during pregnancy remained steady throughout the study period.

The majority of women in the study population used sildenafil (n = 59) or tadalafil (n = 10). In Norway and Sweden, there were fewer than three women who filled prescriptions of vardenafil, and no women used avanafil. The number of pregnant women filling prescriptions for vardenafil and avanafil in the Danish data was fewer than three for each.

Table 1 shows the maternal characteristics by use of any PDE5 inhibitor drug, sildenafil, and tadalafil. Overall, PDE5 inhibitor prescription filling more often occurred before LMP (n = 39; 51%) and in the first trimester (n = 36; 47%). Of all pregnancies with PDE5 inhibitor exposure, 13 (17%) were in mothers who had filled prescriptions only in the second or third trimester. Among pregnant women using any PDE5 inhibitor, 44% were 35 years of age or older, eight had a cardiovascular diagnosis, three specifically had a diagnosis of PAH, and 70% had filled a prescription of another medication. In particular, 16 (21%) women had filled a prescription for cardiovascular drugs.

When collecting information for the indication of PDE5 inhibitor use, there were no reimbursement indications recorded for the filled prescriptions of PDE5 inhibitor in Norway or Denmark. In Sweden, fewer than three women had a diagnosis of PAH, fewer than three woman had Raynaud syndrome, three women had sexual dysfunction written as the reason for prescription, and five women had either filled prescriptions of medication use for infertility treatment, diagnoses of infertility, or the pregnancy was flagged in the MBR as having used assisted reproductive technology.

Among infants prenatally exposed to PDE5 inhibitors, nine were born preterm of which fewer than three were born before 32 weeks of gestation, six were classified as SGA, six were born at moderately low birthweight, and fewer than three at a birthweight lower than 1500 g (Table 2). Five infants had a low Apgar score, 18 were hospitalized in the neonatal intensive care unit, and eight had respiratory and cardiovascular diseases. There were fewer than three stillbirths, no neonatal deaths, and fewer than three post-neonatal deaths among the infants. The number of infants exposed to PDE5 inhibitors anytime during pregnancy remained stable at 2.0–2.5 per 100 000 births from 2006 to the end of the study period.

4 | DISCUSSION

In this population-based study from Scandinavia, use of PDE5 inhibitors during pregnancy was rare; we found 77 exposed among more than 3 million births (2.4 per 100 000). The most frequently used PDE5 inhibitor was sildenafil. PDE5 inhibitor prescription fills most often occurred during the 3 months before the LMP or during the first trimester, with few women filling prescriptions later in pregnancy. Pregnant women using PDE5 inhibitors in our study population were older compared with the general pregnant population in the Nordic countries[18] and had more use of co-medications in pregnancy.[19] A 10-fold increase in use of cardiovascular medications was notable.

The number of infants exposed to PDE5 inhibitors anytime during pregnancy remained stable at 2.0–2.5 per 100 000 births from 2006 to the end of the study period. Infants exposed to PDE5 inhibitors in utero had a shorter gestation and lower birthweight compared with other infants born in the Nordic countries.[18] The proportion of infants classified as SGA was three times higher (7.8% vs. 2.4%) than reported in the general population statistics in Sweden.[20]

Only three of the 77 women had a recorded diagnosis of PAH—the only licensed indication in Scandinavia for PDE5 inhibitor

treatment that occurs in women. Although only a 1-year look back period before pregnancy was used to identify pre-pregnancy maternal diagnoses of severe cardiovascular conditions in the patient registers, we also used diagnoses recorded in the Medical Birth Registers in Sweden and Norway, to ensure that we captured maternal conditions severe enough to be noted and monitored throughout pregnancy. For women with PAH, pregnancy is accompanied by a high risk of severe maternal morbidity and mortality, as well as by fetal death, preterm delivery, and SGA infants. For this reason, such women are followed closely both before and throughout pregnancy by a team of clinical specialists.[21] In women with PAH, sildenafil is commonly continued throughout pregnancy and use of sildenafil and other PDE5 inhibitors in women with PAH may improve pregnancy outcomes, but evidence is limited to case studies and small clinical samples.[22] We explored other possible reasons for PDE5 inhibitor use in this pregnant population using diagnoses and prescription data and found evidence of use for infertility treatment, sexual dysfunction, and Raynaud syndrome.

Similarly, a study by the US Center for Drug Evaluation and Research, using data from the Sentinel Distributed Database, reported that among commercially insured pregnant women PDE5 inhibitor use from LMP to delivery occurred in 2.85 per 100 000 live-birth pregnancies, and was highest among the older mothers: 6.35 and 53.41 per 100 000 live-birth pregnancies in the 35- to 44-year, and 45- to 50-year age groups, respectively. Further, PDE5 inhibitor use more often occurred during the first trimester, and 15.5% of mothers had a diagnosis of PAH. Further, 39% had reproductive diagnoses including infertility and pregnancy complications, 31% pre-eclampsia, 25% fetal growth restriction, 10% cutaneous diagnoses including Raynaud syndrome and wound healing, and 3% had sexual diagnoses.[15]

From the US study and our Scandinavian study, it is evident that the majority of the PDE5 inhibitor use was off-label. Based on completed and ongoing clinical trials and the medical literature, other proposed uses of PDE5 inhibitors are for treatment of infertility,[2–5] sexual dysfunction in women,[23] and Raynaud syndrome.[24] Further, there is evidence that off-label use of sildenafil for treatment for pregnancy complications occurs outside clinical trials, which has spurred the publication of two alerts urging clinicians to stop prescribing sildenafil for fetal growth restriction.[25,26] Additionally, the investigators leading the STRIDER trials noted that a large, multi-center, rigorously designed set of trials, such as theirs, was required to "prevent the persistent 'creep' of the prescription of sildenafil" for the indication of fetal growth restriction.[27] Seventeen per cent of the pregnant women in our study population only had filled prescriptions of PDE5 inhibitors in the second or third trimester of pregnancy. However, from our data, we are unable to determine if PDE5 inhibitors were being used to treat pregnancy complications such as fetal growth restriction or threatened preterm labor.

The current level of evidence on safety in pregnancy is insufficient to provide meaningful clinical decision support. One rodent study has reported evidence of developmental toxicity.[12] Animal studies in rodents and sheep have found adverse cardiovascular effects in the mother and offspring after exposure to sildenafil.[13,14] In humans, an increased risk for neonatal pulmonary hypertension was reported among infants exposed to sildenafil in the Dutch STRIDER trial.[9] However, this study population was composed of high-risk pregnancies complicated by fetal growth restriction, and there are no studies investigating the safety of sildenafil in normal-risk pregnancies. With the controversy and wide media attention surrounding the STRIDER trials, there may be an irrevocable perception of harm of this drug class for pregnant populations, posing challenges for further research in this field.[28] There has been discussion within the scientific community about whether high-risk trials, such as the STRIDER trials, using a drug with an unknown safety profile during pregnancy should have ever been initiated.[29,30] We consider the STRIDER trials to be well-designed with an appropriate interim analysis plan including provision for termination because of safety concerns or evidence of futility of the trial to show a beneficial effect in the primary outcome.[1,9] This highlights the important principal ethical issue of medication use in pregnant women with a lack of safety data. Despite the termination of STRIDER, sildenafil and other PDE5 inhibitors continue to be tested in smaller clinical trials for fetal growth restriction and other pregnancy complications.[6,10,31,32] Whether these trials will be as rigorous in their safety checks, and whether potential positive results will lead the clinical community to embrace this class of drugs for use in pregnancy, is yet to be seen.

The strength of this study was its large size, comprising all singleton births during the study period, and the multinational design. In the Scandinavian countries, the health register data covers nearly the entire population which practically eliminates selection bias. A major limitation was that we did not have precise information on the indication for use of PDE5 inhibitors. As the exposure definition included filled prescriptions within a 90-day window before LMP, exposure misclassification is possible because some women may have discontinued treatment before conception. However, 47% filled a prescription during the first trimester. Records of filled prescriptions do not capture actual consumption. For this reason, we did not know whether, or when, the women actually consumed the PDE5 inhibitors. The Prescribed Drug Registers do not contain information on medication use during inpatient care, and therefore women admitted to hospital during pregnancy and administered PDE5 inhibitors for the first time while there were not identified in our study.

5 | CONCLUSION

The use of PDE5 inhibitors in pregnant women in outpatient settings in the Scandinavian countries is low and has not increased over the last decades. Our findings suggest that they are mostly

prescribed for off-label indications. Use was predominantly in mothers over age 35 years. The safety of fetal exposure to sildenafil and other PDE5 inhibitors in pregnancy has not yet been established. As maternal age continues to increase and additional uses of PDE5 inhibitors are investigated, we highlight the need to support well-defined clinical trials in pregnant women to substantiate safety and efficacy.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

AB, HK, and PK contributed to the concept and design. PK, AE, and AB performed the statistical analysis. All authors contributed to the interpretation of data. CEC, SSC, and HK drafted the manuscript and all authors critically revised the manuscript for important intellectual content.

ORCID

Carolyn E. Cesta https://orcid.org/0000-0001-5759-9366
Silvia Segovia Chacón https://orcid.org/0000-0003-0210-5829
Anders Engeland https://orcid.org/0000-0001-5620-9207
Anne Broe https://orcid.org/0000-0002-4149-8808
Per Damkier https://orcid.org/0000-0003-0591-7187
Kari Furu https://orcid.org/0000-0003-2245-0179
Helle Kieler https://orcid.org/0000-0001-9338-7133
Pär Karlsson https://orcid.org/0000-0002-7177-1713

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