Induction of labour at 41 weeks of gestation versus expectant management and induction of labour at 42 weeks of gestation: A cost-effectiveness analysis

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Abstract
Objective: To assess the cost-effectiveness of induction of labour (IOL) at 41 weeks of gestation compared with expectant management until 42 weeks of gestation.

Design: A cost-effectiveness analysis alongside the Swedish Post-term Induction Study (SWEPIS), a multicentre, randomised controlled superiority trial.

Setting: Fourteen Swedish hospitals during 2016–2018.

Population: Women with an uncomplicated singleton pregnancy with a fetus in cephalic position were randomised at 41 weeks of gestation to IOL or to expectant management and induction at 42 weeks of gestation.

Methods: Health benefits were measured in life years and quality-adjusted life years (QALYs) for mother and child. Total cost per birth was calculated, including healthcare costs from randomisation to discharge after delivery, for mother and child. Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in mean cost between the trial arms by the difference in life years and QALYs, respectively. Sampling uncertainty was evaluated using non-parametric bootstrapping.

Main Outcome Measures: The cost per gained life year and per gained QALY.

Results: The differences in life years and QALYs gained were driven by the difference in perinatal mortality alone. The absolute risk reduction in mortality was 0.004 (from 6/1373 to 0/1373). Based on Swedish life tables, this gives a mean gain in discounted life years and QALYs of 0.14 and 0.12 per birth, respectively. The mean cost per birth was €4108 in the IOL group (n = 1373) and €4037 in the expectant management group (n = 1373), with a mean difference of €71 (95% CI −€232 to €379). The ICER for IOL compared with expectant management was €545 per
INTRODUCTION

Several systematic reviews have shown that induction of labour (IOL) at or beyond term reduces adverse perinatal outcomes, including stillbirth and neonatal death, without increasing the rate of caesarean deliveries, compared with expectant management until 42 weeks of gestation and beyond.1-3 Hence, several national guidelines now recommend IOL from 41 weeks of gestation compared with the previous recommendation at 42 weeks of gestation.4-6

The Swedish Post-term Induction Study (SWEPIS), a recent large multicentre randomised controlled superiority trial comparing IOL at 41 weeks of gestation with expectant management until 42 weeks of gestation, demonstrated no significant difference in the primary composite outcome (perinatal mortality and morbidity), but reported significantly lower perinatal mortality in the IOL group.7 The caesarean delivery rate did not differ between groups. However, a consequence of a shift in policy to IOL at 41 weeks of gestation could confer an increase in workload at the delivery wards and result in a substantial increase in costs for the healthcare system, given that up to approximately 20% of the pregnant population will be involved.8

In a systematic literature search we identified two studies evaluating health economics aspects of IOL at 41 weeks of gestation compared with expectant management until 42 weeks of gestation or beyond (Appendix S1). In a study by Goeree et al., based on The Canadian Multicentre Post-term Pregnancy Trial from 1992, IOL was C$193 cheaper compared with expectant management in a ‘cost-minimisation’ analysis.9,10

The study by Kaimal et al. was based on a cost-effectiveness decision-analytic model and concluded that IOL was cost-effective.11

The aim of this study was to evaluate the total cost per birth and cost-effectiveness within SWEPIS, including costs for the woman and her child.7

METHODS

This was a pre-planned cost-effectiveness study within SWEPIS,7 a multicentre, open-label, randomised controlled superiority trial comparing IOL at 41 weeks of gestation with expectant management until 42 weeks of gestation.

2.1 | Trial design

2.1.1 | Participants

Full details of SWEPIS are presented elsewhere.7 Briefly, SWEPIS planned to recruit 10 038 women but was halted after the inclusion of 2760 women, for safety reasons (with six perinatal deaths in the expectant management group and no perinatal deaths in the IOL group). Inclusion criteria were uncomplicated singleton pregnancies and a live fetus in cephalic presentation between 40+6 and 41+1 weeks of gestation. Exclusion criteria were previous caesarean delivery or other major uterine surgery, insulin-dependent diabetes, hypertensive disorder of pregnancy, known oligohydramnios or small-for-gestational-age fetus, diagnosed fetal malformation and contraindication to vaginal delivery.

2.1.2 | Intervention

Women were randomised with a 1:1 allocation to either IOL at 410-2 weeks of gestation (n = 1381) or expectant management until 420-1 weeks of gestation (n = 1379). Fetal surveillance in the expectant management group was performed according to local protocols. This generally included routine outpatient visits with auscultation of the fetal heart rate by Doppler fetal monitor, measurement of blood pressure and fundal height, and unanticipated visits to antenatal care where further examinations, IOL or caesarean delivery were initiated for usual obstetric indications. Women in both groups were induced according to local protocols.
2.2 | Measuring health outcomes

The cost-effectiveness analysis was performed based on life years and quality-adjusted life years (QALYs) as health outcomes. The life years for the children were measured based on differences in perinatal mortality (mortality comprising stillbirth and neonatal mortality, days 0–27) multiplied by Swedish survival probabilities as taken from life-table statistics. QALYs for the children were calculated by adjusting the survival probabilities for each future life year by the mean (Swedish population) health-related quality of life score at each age. For QALY calculations for the women, potential health-related quality of life effects were assessed by means of the EuroQol 5-dimension (EQ-5D) measure at randomisation and at 3 months after delivery. The EQ-5D assesses mobility, self-care, usual activity, pain/discomfort and anxiety/depression, and was assessed in a subpopulation of women participating in SWEPIS at three centres representing two university hospitals (Sahlgrenska University Hospital and Örebro University Hospital) and one county hospital (Falu Hospital).

2.3 | Total costs and cost-effectiveness analysis

We applied a strict healthcare perspective to the analysis: only healthcare costs up to discharge from the delivery stay were included. Health outcome consequences beyond the first year were discounted at a 3% rate, i.e. future consequences were given less weight than those occurring in the first year, in line with general recommendations such as those from the US Panel on Cost-Effectiveness in Health and Medicine. Sensitivity analyses were carried out with discount rates at 1.5 and 5%.

2.4 | Measuring costs

The total cost per birth from randomisation to discharge after delivery for both mother and child was calculated and included: (i) costs associated with the delivery, from admittance to discharge; (ii) costs for outpatient visits and inpatient stay between randomisation and admittance to the delivery ward; (iii) costs for neonatal intensive care unit (NICU) (in association with the delivery, inpatient stay and/or home care).

The costs were collected from the accounting department from each centre. They were calculated using a system called cost per patient (CPP) developed by the Swedish Association of Local Authorities and Regions. CPP reports a fixed and a variable cost per patient. The fixed cost includes cost for staffing, rent, everyday materials, depreciation and everyday laboratory costs, per patient and per care episode. The variable cost includes costs for the operating theatre and/or intensive care unit, and additional costs for advanced laboratory work and imaging diagnostics, for example. The fixed costs are presented as a standardised cost per day and are also given as standardised costs per care given, both intrapartum and postpartum, during the hospital stay. All costs are presented in Euro (€ = 10.27 SEK).

2.5 | Robustness analysis

A robustness analysis of the total cost per birth and cost-effectiveness was carried out on women randomised and delivered at Sahlgrenska University Hospital, Gothenburg, where the costs associated with delivery were based on the cost per hour for care at the delivery and in the postpartum ward, respectively. Costs for outpatient visits and NICU were the same as used in the main analysis. These data were only available for women giving birth at Sahlgrenska University Hospital.

The analysis was performed in order to get a more precise cost compared with the CPP model. In the CPP model, costs are standardised per delivery stay, regardless of whether the women and/or infant stayed on the delivery ward, with higher staffing and more resources, or on the postpartum ward, with less staffing and resources, and was calculated per day. In the robustness analysis we separated the total hospital stay for delivery into time spent on the delivery ward (in hours) and time spent on the postpartum ward (in hours). The clinical routine was to stay on the delivery ward during the whole induction process until 2 hours after the delivery. A cost per hour was then applied to the time spent on the delivery ward and on the postpartum ward, respectively.

2.6 | Statistical analysis

The analysis was made on the intention-to-treat population. Each woman was assessed in the group that she was allocated to at randomisation, regardless of which intervention she received after that.

The difference in arithmetic mean cost between groups was estimated by means of linear regression analysis for the total cost per birth, cost per delivery, cost for care at NICU and cost for outpatient visits. The healthcare cost data are skewed to the right and therefore standard errors and 95% CIs were based on non-parametric bootstrapping. P < 0.05 was considered statistically significant.

The incremental cost-effectiveness ratios (ICERs) were calculated as the ratio of difference in arithmetic mean costs and difference in arithmetic mean life years as well as OALYs. Fieller’s theorem was used to construct 95% CIs for the ICERs. We also present a cost-effectiveness acceptability curve (CEAC), which calculates the probability that the ICER is below varying cost-effectiveness threshold levels. The threshold currently set by the Swedish National Board of Health and Welfare for willingness to pay is 500 000 SEK (about €50 000) per QALY.

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2.7 | Core outcome set

A core outcome set (COS) according to the Core Outcomes in Women's and Newborn Health (CROWN) initiative was not used. A COS for IOL or health economic assessment was not available when designing the trial.

2.8 | Patient and public involvement

There was no public or patient involvement in this trial.

3 | RESULTS

Figure S1 shows the progress of women through the study. The cost calculations were based on 2746 participants (1373 in each group), representing 99.5% of the SWEPIS population. For 14 women and their infants the costs could not be retrieved: eight in the IOL group and six in the expectant management group. None of these had a primary outcome or an infant treated in NICU. One woman in the IOL group and two women in the expectant management group had a caesarean delivery. The mean hospital stay of these women was 2.7 days in both groups. Baseline characteristics were comparable between the groups (Table S1).

3.1 | Health outcome

Perinatal, delivery and maternal outcomes are presented in Tables S2–S4. The primary outcome (a composite of perinatal mortality and severe neonatal morbidity) did not differ between groups (2.4%, 33/1373, versus 2.3%, 31/1373; \(P = 0.90\)). However, perinatal mortality differed significantly with no deaths in the IOL group and six deaths in the expectant management group (0.0%, 0/1373, versus 0.4%, 6/1373; \(P = 0.03\)). Admission to NICU was significantly lower in the IOL group (4.0%, 55/1373, versus 6.0%, 82/1373; \(P = 0.02\)). Based on the results from SWEPIS on perinatal morality (Table S3), the absolute risk reduction in mortality was 0.004 (from 6/1373 to 0/1373) and based on Swedish life tables, this gives a gain in mean discounted life years and QALYs of 0.14 life years and 0.12 QALYs per birth, respectively. The health-related quality of life (and associated QALYs) for the mothers did not differ substantially between the groups (QALY difference 0.0016; \(P = 0.17\)) and the gains in life years and QALYs are thus only driven by differences in perinatal mortality.

3.2 | Cost results

The incremental total cost per birth for the IOL group versus the expectant management group was not significant (€71, 95% CI €−135 to €278), although the subcomponents of the total cost differed significantly between the groups: delivery costs were €342 more expensive in the IOL group (95% CI €184–501); NICU costs were €205 lower in the IOL group (95% CI −€343 to −€67); and costs for outpatients visits and inpatient stay after randomisation, but before delivery, were also lower in the IOL group (−€66, 95% CI −€76 to −€56) (Table 1).

Robustness analysis was conducted for 697 women and their infants from Sahlgrenska University Hospital, Gothenburg (79 women were excluded from the analysis, mainly for a lack of registered exact time of discharge, evenly distributed between the groups). The incremental total cost per birth was significantly higher in the IOL group (€456, 95% CI €23–890). The delivery cost was €596 higher in the IOL group (95% CI €198–994) and the costs for outpatient visits and inpatient stay after randomisation, but before delivery, were also lower in the IOL group (−€66, 95% CI −€76 to −€56) (Table 1).

### Table 1

Mean cost per birth in Euros (95% CI) of induction of labour compared with expectant management

| Treatment                          | Delivery costs\(^a\) Mean (95% CI) | NICU costs\(^b\) Mean (95% CI) | Costs for outpatient visits and inpatient stay\(^c\) Mean (95% CI) | Total cost per birth Mean (95% CI) |
|-----------------------------------|-----------------------------------|---------------------------------|-----------------------------------------------------------------|----------------------------------|
| Main analysis                     |                                   |                                 |                                                                 |                                  |
| Induction of labour (\(n = 1373\))| 3911 (3797–4026)                  | 175 (101–248)                  | 22 (18–27)                                                    | 4108 (3966–4251)                 |
| Expectant management (\(n = 1373\))| 3569 (3455–3683)                  | 380 (249–510)                  | 89 (80–97)                                                    | 4037 (3594–4217)                 |
| Incremental cost\(^d\)            | 342 (184–501)                     | −205 (−343 to −67)            | −66 (−76 to −56)                                              | 71 (−135 to 278)                 |
| Robustness analysis\(^d\)         |                                   |                                 |                                                                 |                                  |
| Induction of labour, \(n = 349\)  | 4180 (3921–4440)                  | 171 (3–344)                   | 12 (7–16)                                                     | 4363 (4044–4681)                 |
| Expectant management, \(n = 348\) | 3584 (3288–3881)                  | 232 (105–361)                  | 89 (76–102)                                                   | 3906 (3564–4248)                 |
| Incremental cost\(^d\)            | 596 (198–994)                     | −62 (−274 to 150)            | −78 (−90 to −65)                                              | 456 (23–890)                     |

Note: 95% CIs for the incremental cost are based on bootstrapped bias-corrected standard errors (1€ = 10.27 SEK).

\(^a\)From admittance to discharge, per delivery.

\(^b\)In- and outpatient care costs associated with the delivery occasion, per infant.

\(^c\)After randomisation but before delivery, per delivery.

\(^d\)Based on the Sahlgrenska University Hospital population.

\(^e\)Induction of labour versus expectant management.
visits and inpatient stay were €78 lower (95% CI −€90 to −€65). The costs for admission to the NICU did not differ: €62 (95% CI −€274 to €150) (1).

### 3.3 | Cost-effectiveness results

The cost-effectiveness analysis is presented in Table 2.

The ICER per life year with IOL at 41 weeks of gestation compared with expectant management until 42 weeks of gestation was €524, with a 95% CI ranging from being dominant, i.e. with both lower costs and better health outcomes (more life years), to €3664 per gained life year. The ICER per gained QALY was €601, with the 95% CI ranging from being dominant (i.e. lower costs and more QALYs) to €4199 per gained QALY.

The impact of the discount rate is modest in absolute terms. The cost per QALY with discount rates of 1.5% and 5.0% are €394 per QALY and €905 per QALY, respectively.

The results from the robustness analysis based on cost data from Sahlgrenska University Hospital indicate a higher ICER, at €2389 per life year (95% CI ranging from dominant, with lower costs and more life years, to €6632 per life year gained) and €2736 per QALY (95% CI ranging from dominant, with lower costs and more QALYs, to €7600 per QALY gained) (Table 2).

### 3.4 | Assessing uncertainty in the estimate of ICER

To assess the sampling uncertainty, we also present results from non-parametric bootstrapping (using 1000 bootstrap replicates on incremental costs) and simulations (on incremental QALYs) in the form of a cost-effectiveness plane and a CEAC. The cost-effectiveness plane is presented in Figure 1, where 74% of the ICERs are in the north-eastern quadrant (i.e. more expensive and better health outcomes).

### TABLE 2  Cost-effectiveness analysis of induction of labour compared with expectant management

| Treatment                                      | Incremental life years | Incremental QALYs | ICER per life year | ICER per QALY |
|-----------------------------------------------|------------------------|-------------------|--------------------|--------------|
| Main analysis                                 |                        |                   |                    |              |
| Induction of labour (n = 1373) versus         | 0.14 (0.03–0.24)       | 0.12 (0.02–0.22)  | €524/life year     | €601/QALY    |
| expectant management (n = 1373)                |                        |                   | (dominant to €3664)| (dominant to €4199) |
| Robustness analysis b                         |                        |                   |                    |              |
| Induction of labour (n = 349) versus           | 0.19 (0.09–0.30)       | 0.17 (0.07–0.26)  | €2389/life year    | €2736/QALY   |
| expectant management (n = 348)                 |                        |                   | (dominant to €6632)| (dominant to €7600) |

Note: 95% CIs for the cost-effectiveness ratios are based on non-parametric bootstrapping.

*Per birth.

Based on the Sahlgrenska University Hospital population, perinatal mortality 0/349 versus 2/348.

### FIGURE 1  Cost-effectiveness plane, with incremental costs and QALYs
and 25% are found in the south-eastern quadrant (i.e. less expensive and better health outcomes: ‘dominant’). Only 1% of the ICERs are ‘dominated’, i.e. indicating higher costs and worse health outcomes (north-western quadrant) for the intervention (IOL at 41 weeks of gestation versus expectant management until 42 weeks of gestation). No ICERs are in the southwest quadrant (less expensive and worse health).

In Figure 2 a CEAC is presented, plotting the probability that IOL is cost-effective for a variety of ‘threshold values’ for decision maker willingness to pay per QALY gained. At a threshold level of €10 000/QALY, the probability that IOL at 41 weeks of gestation is cost-effective is 0.988 (98.8%).

4 | DISCUSSION

4.1 | Main findings

Based on the reduction in perinatal mortality, total life years and QALYs were higher in the IOL group and the cost per life year and QALY was lower in the IOL group. The Swedish National Board of Health and Welfare considers costs of about €50 000 as a threshold for high cost per QALY and the National Institute for Health and Care Excellence in the UK, considered to be one of the most conservative high-income countries, recommends costs below €21 750–32 635 per QALY. The cost per QALY in our study, using costs in Sweden, was well below these thresholds, indicating that IOL at 41 weeks of gestation is cost-effective.

When exploring sampling uncertainty based on a non-parametric bootstrap method, most of the bootstrapped ICERs were found to show modestly higher costs and better health outcomes (74%) or reduced costs and better health outcomes (25%) for the intervention (IOL at 41 weeks of gestation). The CEAC showed a 99% likelihood that IOL is cost-effective at a threshold value of €10 000 per QALY.

The total cost per birth for IOL was not significantly higher compared with that for expectant management. However, each subcomponent of the total cost significantly differed between the strategies. The largest expense was the delivery cost and this was more expensive in the IOL group.

In the robustness analysis, where more precise cost data for delivery were used, the cost per life year and QALY gained were still below the commonly used threshold values in Swedish health policy decision making.19

4.2 | Strength and limitations

A strength of this study was that it is based on one large randomised controlled trial (SWEPIS) conducted in the real delivery/NICU context with a low number of participants lost to follow-up (0.5%).7 In addition, the results of SWEPIS were in agreement with those reported by other recently published randomised controlled trials and systematic reviews.3,21-23 Lastly, the robustness analysis, where we separated the delivery hospital stay into time spent at the high-cost delivery ward and time spent at the low-cost postpartum ward, in order to get a more precise cost, confirmed the main analysis.

One limitation in this study was the early termination of SWEPIS for safety reasons (with higher perinatal mortality rate in the expectant management group), introducing an uncertainty of the magnitude of the decrease of perinatal mortality in the IOL group.7 The impact on the interpretation of the results is difficult to assess, as there is inconsistency in
4.3 | Interpretation

Two earlier studies have assessed the health economic aspects of IOL at 41 weeks of gestation compared with expectant management until 42 weeks of gestation or beyond. Goeree et al. concluded that the IOL regimen was C$193 cheaper (a minimisation analysis). In a decision-analytic model, Kaimal et al. showed IOL to be cost-effective with a cost per QALY of $10,945 (96% probability at a threshold value of $50,000 per QALY).11

In Walker et al., an economic evaluation alongside a randomised controlled trial (including 61% of the trial participants, n = 380) comparing IOL at 39 weeks of gestation with expectant management until 41 weeks of gestation in healthy women aged ≥35 years, the IOL cost was £236 lower compared with expectant management, resulting in an ICER of −£114,525.31 Furthermore, Einarson et al. presented a healthcare cost analysis based on a subset of women enrolled in the ARRIVE trial (A Randomized Trial of Induction Versus Expectant Management) (including 20% of the ARRIVE population, n = 1201) comparing IOL at 39 weeks of gestation with expectant management until 41 weeks of gestation in nulliparous women with a low-risk pregnancy.22,32 They concluded that the total costs were similar in the two groups. They found an increase in intrapartum and delivery costs in the IOL group but a decrease in outpatient antenatal costs, in agreement with our findings. In addition, Grobman et al. reported, also on the ARRIVE population (n = 6106), a lower frequency of antenatal visits, treatments and tests, a longer duration of labour, but a shorter postpartum stay in the IOL group, and concluded that IOL can be performed without increasing the use of healthcare resources.33 In contrast, after the ARRIVE trial was published, Hersh et al. used a cost-effectiveness model based on a theoretical cohort of 1.6 million women comparing IOL at 39 weeks of gestation in nulliparous women with low-risk pregnancies with expectant management until 41 weeks of gestation, and presented a marginally cost-effective ICER of $87,692 per QALY (with a willingness-to-pay threshold of $100,000). They concluded that IOL will lead to improved outcomes, but increased costs. The same research group also published maternal and neonatal hospitalisation costs in California based on a retrospective birth cohort from 2007 to 2011 (n = 1,278,151) of IOL in low-risk pregnancies compared with those being admitted for spontaneous labour.35 An increase in maternal median hospitalisation costs in the IOL group but a decrease in neonatal median hospitalisation costs were found. However, comparing IOL with spontaneous labour, i.e. two types of onset of labour, differs from comparing IOL and expectant management, e.g. two management strategies. The caesarean delivery rate is important when assessing IOL compared with expectant management in cost-effectiveness analyses. The perception that IOL increases the caesarean delivery rate has prevailed.36 One study comparing IOL at term with expectant management until 42 weeks of gestation in a decision-analytic model concluded that IOL resulted in an increase in caesarean deliveries and was more expensive.37 Most, but not all, recent systematic reviews on IOL versus expectant management at term or beyond in uncomplicated pregnancies demonstrate no difference, or a decrease, in caesarean deliveries with IOL.1,3,36,38,39 In Kaimal et al., several different scenarios were conducted regarding the rate of caesarean delivery in the IOL group and even with a 47% increase in caesarean deliveries the IOL regimen would still be cost-effective.11 Our study showed a similar number of caesarean deliveries, operative vaginal deliveries, adverse perinatal outcomes (except perinatal mortality) and maternal outcomes, such as postpartum haemorrhage and perineal tears, in respective groups. Hence, in our study the difference in total costs per delivery stay was not driven by these outcomes but by the time spent in the hospital. In addition, there is scope for a possible increase in caesarean delivery in the IOL group, not considering any potential costs for an increase in placenta accreta spectrum disorders associated with caesarean delivery, before it would be regarded as not cost-effective to induce labour at 41 weeks of gestation.

We did not consider cost after discharge from the delivery stay. Callander et al. assessed the cost of stillbirth in Australia (QALYs and life years gained excluded).40 They included all healthcare costs during the first 2 years after delivery and...
showed an increase in costs of 3744 Australian dollars (approximately €2312) for women with stillborn babies compared with a control group with liveborn babies. Thus, the costs in the expectant management group would probably have been higher with a longer follow-up time in our study.

A possible management approach to decrease the costs of IOL might be outpatient IOL. However, there are conflicting results regarding the cost-effectiveness of outpatient IOL and its safety must be clarified.41

5 | CONCLUSION

Induction of labour at 41 weeks of gestation results in a better health outcome and in no significant difference in costs. IOL is thus cost-effective compared with expectant management until 42 weeks of gestation using standard threshold values for acceptable cost per life years and QALYs.

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CONFLICT OF INTEREST

Dr. Carlsson reports that she is part of a research project planning an RCT concerning outpatient induction - the OPTION study. No other authors have anything to disclose. Completed disclosure of interests form available to view on -line as supporting information.

AUTHOR CONTRIBUTIONS

MA is the first author. UBW, HH, VS, MS and HE conceived and designed the study. MA, SS, MJ, JW, HF and Anna Hagman, senior consultant at North Ålvsborg Hospital, Trollhättan, oversaw the collection of data at the local centres. MA, UBW, HH, LL, CB and MS wrote the statistical analysis plan. MA and UBW performed the data cleaning together with MS. MS performed the analysis. MA, UBW, HH, LL, VS, YC and HE interpreted the data. MA, UBW and MS wrote the first draft of the article, which was then critically reviewed and revised by the other co-authors. MS is the senior author. All authors approved the final version of the article for publication. UBW and HH are guarantors. All authors had full access to all data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. The corresponding author attests that all listed authors meet the requirements for authorship and that no others meeting the criteria have been omitted.

ETHICAL APPROVAL

This study was approved by the regional ethics board in Gothenburg in May 2014 (Dnr: 285-14) as well as these complementary applications (T 905-15, T 291-16, T 1180-16, T 330-17, T 1066-17, T 087-18, T 347-18, T 961-18, T 1110-18). All participants gave informed written consent before taking part in the study.

DATA AVAILABILITY STATEMENT

Data are available from the corresponding author, upon reasonable request.

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